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(54) Title: HETEROARYL-PHENYL SUBSTITUTED FACTOR XA INHIBITORS

(57) Abstract: The present application describes heteroaryl-phenyl substituted compounds and derivatives thereof, or pharmaceutically acceptable salt or prodrug forms thereof, which are useful as inhibitors of factor Xa.



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TITLE

Heteroaryl-Phenyl Substituted Factor Xa Inhibitors

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FIELD OF THE INVENTION

This invention relates generally to heteroaryl-phenyl substituted compounds and derivatives thereof, which are inhibitors of trypsin-like serine protease enzymes, especially factor Xa, pharmaceutical compositions containing the same, and methods of using the same as anticoagulant agents for treatment and prevention of thromboembolic disorders.

BACKGROUND OF THE INVENTION

15

Activated factor Xa, whose major practical role is the generation of thrombin by the limited proteolysis of prothrombin, holds a central position that links the intrinsic and extrinsic activation mechanisms in the final common pathway of blood coagulation. The generation of thrombin, the final serine protease in the pathway to generate a fibrin clot, from its precursor is amplified by formation of prothrombinase complex (factor Xa, factor V, Ca^{2+} and phospholipid). Since it is calculated that one molecule of factor Xa can generate 138 molecules of thrombin (Elodi, S., Varadi, K.: Optimization of conditions for the catalytic effect of the factor IXa-factor VIII Complex: Probable role of the complex in the amplification of blood coagulation. *Thromb. Res.* **1979**, 15, 617-629), inhibition of factor Xa may be more efficient than inactivation of thrombin in interrupting the blood coagulation system.

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Therefore, efficacious and specific inhibitors of factor Xa are needed as potentially valuable therapeutic agents for the treatment of thromboembolic disorders. It is thus desirable to discover new factor Xa inhibitors.

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SUMMARY OF THE INVENTION

Accordingly, one object of the present invention is to provide novel heteroaryl-phenyl substituted compounds and derivatives thereof that are useful as factor Xa inhibitors or pharmaceutically acceptable salts or prodrugs thereof.

It is another object of the present invention to provide pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

It is another object of the present invention to provide a method for treating thromboembolic disorders comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

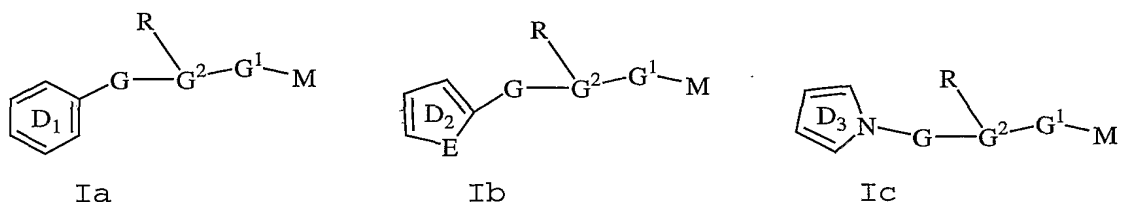
It is another object of the present invention to provide novel heteroaryl-phenyl substituted compounds for use in therapy.

It is another object of the present invention to provide the use of novel heteroaryl-phenyl substituted compounds for the manufacture of a medicament for the treatment of a thromboembolic disorder.

These and other objects, which will become apparent during the following detailed description, have been achieved by the inventors' discovery that the presently claimed heteroaryl-phenyl substituted compounds and derivatives thereof, or pharmaceutically acceptable salt or prodrug forms thereof, are effective factor Xa inhibitors.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[1] Thus, in a first embodiment, the present invention provides a novel compound of formula Ia, Ib, or Ic:



or a stereoisomer or pharmaceutically acceptable salt

5 thereof, wherein;

ring D₁ is selected from pyridine, pyrazine, pyridazine, and pyrimidine and is substituted with 1 R^a and 0-1 R^b;

10 ring D₂ is a 5-membered heteroaromatic ring system comprising E, carbon atoms, and 0-3 N atoms, wherein E is selected from O, S, and N-R^c and ring D₂ is substituted with 1 R^a and 0-1 R^b;

15 ring D₃ is a 5-membered heteroaromatic ring system comprising carbon atoms and from 0-3 additional N atoms and ring D₃ is substituted with 1 R^a and 0-1 R^b;

R is selected from H, C₁₋₄ alkyl, F, Cl, Br, I, OH, OCH₃,
 20 OCH₂CH₃, OCH(CH₃)₂, OCH₂CH₂CH₃, CN, C(=NR⁸)NR⁷R⁹,
 NHC(=NR⁸)NR⁷R⁹, NR⁸CH(=NR⁷), NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃
 alkyl)₂, C(=NH)NH₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), CH₂N(C₁₋₃
 alkyl)₂, CH₂CH₂NH₂, CH₂CH₂NH(C₁₋₃ alkyl), CH₂CH₂N(C₁₋₃
 alkyl)₂, (CR⁸R⁹)_tNR⁷R⁸, (CR⁸R⁹)_tC(O)NR⁷R⁸, and OCF₃;

25 R^a is selected from H, C₁₋₄ alkyl, F, Cl, Br, I, OH, OCH₃,
 OCH₂CH₃, OCH(CH₃)₂, OCH₂CH₂CH₃, CN, C(=NR⁸)NR⁷R⁹,
 NHC(=NR⁸)NR⁷R⁹, NR⁸CH(=NR⁷), NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃
 alkyl)₂, C(=NH)NH₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), CH₂N(C₁₋₃
 30 alkyl)₂, CH₂CH₂NH₂, CH₂CH₂NH(C₁₋₃ alkyl), CH₂CH₂N(C₁₋₃
 alkyl)₂, (CR⁸R⁹)_tNR⁷R⁸, (CR⁸R⁹)_tC(O)NR⁷R⁸, and OCF₃;

R^b is selected from H, C_{1-4} alkyl, F, Cl, Br, I, OH, OCH_3 ,
 OCH_2CH_3 , $OCH(CH_3)_2$, $OCH_2CH_2CH_3$, CN, $C(=NR^8)NR^7R^9$,
 $NHC(=NR^8)NR^7R^9$, $NR^8CH(=NR^7)$, NH_2 , $NH(C_{1-3} \text{ alkyl})$, $N(C_{1-3}$
5 $\text{alkyl})_2$, $C(=NH)NH_2$, CH_2NH_2 , $CH_2NH(C_{1-3} \text{ alkyl})$, $CH_2N(C_{1-3}$
 $\text{alkyl})_2$, $CH_2CH_2NH_2$, $CH_2CH_2NH(C_{1-3} \text{ alkyl})$, $CH_2CH_2N(C_{1-3}$
 $\text{alkyl})_2$, $(CR^8R^9)_tNR^7R^8$, $(CR^8R^9)_tC(O)NR^7R^8$, and OCF_3 ;

R^c is selected from H, C_{1-4} alkyl, OCH_3 , OCH_2CH_3 , $OCH(CH_3)_2$,
10 $OCH_2CH_2CH_3$, NH_2 , $NH(C_{1-3} \text{ alkyl})$, $N(C_{1-3} \text{ alkyl})_2$,
 $C(=NH)NH_2$, CH_2NH_2 , $CH_2NH(C_{1-3} \text{ alkyl})$, $CH_2N(C_{1-3} \text{ alkyl})_2$,
 $CH_2CH_2NH_2$, $CH_2CH_2NH(C_{1-3} \text{ alkyl})$, $CH_2CH_2N(C_{1-3} \text{ alkyl})_2$,
 $(CR^8R^9)_tNR^7R^8$, $(CR^8R^9)_tC(O)NR^7R^8$, and OCF_3 ;

15 G is absent or is selected from CH_2 , $C(O)$, O , NR^3 , $S(O)_p$,
 CH_2CH_2 , $C(O)CH_2$, $CH_2C(O)$, OCH_2 , CH_2O , NR^3CH_2 , CH_2NR^3 ,
 $S(O)_pCH_2$, $CH_2S(O)_p$, $CH_2CH_2CH_2$, $C(O)CH_2CH_2$, $CH_2C(O)CH_2$,
 $CH_2CH_2C(O)$, OCH_2CH_2 , CH_2OCH_2 , CH_2CH_2O , $NR^3CH_2CH_2$, $CH_2NR^3CH_2$,
 $CH_2CH_2NR^3$, $S(O)_pCH_2CH_2$, $CH_2S(O)_pCH_2$, and $CH_2CH_2S(O)_p$;

20

G_1 is absent or is selected from $(CR^3R^{3a})_{1-5}$,
 $(CR^3R^{3a})_{0-2}CR^3=CR^3(CR^3R^{3a})_{0-2}$, $(CR^3R^{3a})_{0-2}C\equiv C(CR^3R^{3a})_{0-2}$,
 $(CR^3R^{3a})_uC(O)(CR^3R^{3a})_w$, $(CR^3R^{3a})_uC(O)O(CR^3R^{3a})_w$,
 $(CR^3R^{3a})_uOC(O)(CR^3R^{3a})_w$, $(CR^3R^{3a})_uO(CR^3R^{3a})_w$,
25 $(CR^3R^{3a})_uNR^3(CR^3R^{3a})_w$, $(CR^3R^{3a})_uC(O)NR^3(CR^3R^{3a})_w$,
 $(CR^3R^{3a})_uNR^3C(O)(CR^3R^{3a})_w$, $(CR^3R^{3a})_uOC(O)NR^3(CR^3R^{3a})_w$,
 $(CR^3R^{3a})_uNR^3C(O)O(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^3C(O)NR^3(CR^3R^{3a})_w$,
 $(CR^3R^{3a})_uNR^3C(S)NR^3(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(CR^3R^{3a})_w$,
 $(CR^3R^{3a})_uS(O)(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(O)_2(CR^3R^{3a})_w$,
30 $(CR^3R^{3a})_uS(O)NR^3(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^3S(O)_2(CR^3R^{3a})_w$,
 $(CR^3R^{3a})_uS(O)_2NR^3(CR^3R^{3a})_w$, and $(CR^3R^{3a})_uNR^3S(O)_2NR^3(CR^3R^{3a})_w$,
wherein $u + w$ total 0, 1, 2, 3, or 4, provided that G_1
does not form a N-N, N-O, N-S, NCH_2N , NCH_2O , or NCH_2S
bond with either group to which it is attached;

G² is phenyl, naphthyl, or a 5-10 membered heteroaryl consisting of carbon atoms and from 1-3 heteroatoms selected from N, O, and S;

5

M is isoxazoline, pyrazoline, isothiazoline, triazoline, tetrazoline, phenyl, or a 5-6 membered aromatic heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from O, N, and S, and is substituted with -Z-A-B;

10

M is also substituted with 0-2 R^{1a};

Z is selected from a bond, $-(\text{CR}^2\text{R}^{2a})_{1-4}-$, $(\text{CR}^2\text{R}^{2a})_q\text{O}(\text{CR}^2\text{R}^{2a})_{q^1}$,
 15 $(\text{CR}^2\text{R}^{2a})_q\text{NR}^3(\text{CR}^2\text{R}^{2a})_{q^1}$, $(\text{CR}^2\text{R}^{2a})_q\text{C}(\text{O})(\text{CR}^2\text{R}^{2a})_{q^1}$,
 $(\text{CR}^2\text{R}^{2a})_q\text{C}(\text{O})\text{O}(\text{CR}^2\text{R}^{2a})_{q^1}$, $(\text{CR}^2\text{R}^{2a})_q\text{OC}(\text{O})(\text{CR}^2\text{R}^{2a})_{q^1}$,
 $(\text{CR}^2\text{R}^{2a})_q\text{C}(\text{O})\text{NR}^3(\text{CR}^2\text{R}^{2a})_{q^1}$, $(\text{CR}^2\text{R}^{2a})_q\text{NR}^3\text{C}(\text{O})(\text{CR}^2\text{R}^{2a})_{q^1}$,
 $(\text{CR}^2\text{R}^{2a})_q\text{OC}(\text{O})\text{O}(\text{CR}^2\text{R}^{2a})_{q^1}$, $(\text{CR}^2\text{R}^{2a})_q\text{OC}(\text{O})\text{NR}^3(\text{CR}^2\text{R}^{2a})_{q^1}$,
 $(\text{CR}^2\text{R}^{2a})_q\text{NR}^3\text{C}(\text{O})\text{O}(\text{CR}^2\text{R}^{2a})_{q^1}$, $(\text{CR}^2\text{R}^{2a})_q\text{NR}^3\text{C}(\text{O})\text{NR}^3(\text{CR}^2\text{R}^{2a})_{q^1}$,
 20 $(\text{CR}^2\text{R}^{2a})_q\text{S}(\text{CR}^2\text{R}^{2a})_{q^1}$, $(\text{CR}^2\text{R}^{2a})_q\text{S}(\text{O})(\text{CR}^2\text{R}^{2a})_{q^1}$,
 $(\text{CR}^2\text{R}^{2a})_q\text{S}(\text{O})_2(\text{CR}^2\text{R}^{2a})_{q^1}$, $(\text{CR}^2\text{R}^{2a})_q\text{SO}_2\text{NR}^3(\text{CR}^2\text{R}^{2a})_{q^1}$,
 $(\text{CR}^2\text{R}^{2a})_q\text{NR}^3\text{SO}_2(\text{CR}^2\text{R}^{2a})_{q^1}$, and $(\text{CR}^2\text{R}^{2a})_q\text{NR}^3\text{SO}_2\text{NR}^3(\text{CR}^2\text{R}^{2a})_{q^1}$,
 wherein $q + q^1$ total 0, 1, or 2, provided that Z does not form a N-N, N-O, N-S, NCH₂N, NCH₂O, or NCH₂S bond
 25 with either group to which it is attached;

R^{1a} is selected from H, $-(\text{CH}_2)_x\text{-R}^{1b}$, $-\text{CH}=\text{CH-R}^{1b}$, $\text{NCH}_2\text{R}^{1c}$,
 $\text{OCH}_2\text{R}^{1c}$, $\text{SCH}_2\text{R}^{1c}$, $\text{NH}(\text{CH}_2)_2(\text{CH}_2)_t\text{R}^{1b}$, $\text{O}(\text{CH}_2)_2(\text{CH}_2)_t\text{R}^{1b}$,
 $\text{S}(\text{CH}_2)_2(\text{CH}_2)_t\text{R}^{1b}$, $\text{S}(\text{O})_p(\text{CH}_2)_r\text{R}^{1d}$, $\text{O}(\text{CH}_2)_r\text{R}^{1d}$, $\text{NR}^3(\text{CH}_2)_r\text{R}^{1d}$,
 30 $\text{OC}(\text{O})\text{NR}^3(\text{CH}_2)_r\text{R}^{1d}$, $\text{NR}^3\text{C}(\text{O})\text{NR}^3(\text{CH}_2)_r\text{R}^{1d}$, $\text{NR}^3\text{C}(\text{O})\text{O}(\text{CH}_2)_r\text{R}^{1d}$,
 and $\text{NR}^3\text{C}(\text{O})(\text{CH}_2)_r\text{R}^{1d}$, provided that R^{1a} forms other than an N-halo, N-N, N-S, N-O, or N-CN bond;

alternatively, when two R^{1a} 's are attached to adjacent atoms, together with the atoms to which they are attached they form a 5-7 membered ring consisting of: carbon atoms and 0-2 heteroatoms selected from the group consisting of N, O, and $S(O)_p$, this ring being substituted with 0-2 R^{4b} and comprising: 0-3 double bonds;

R^{1b} is selected from H, C_{1-3} alkyl, F, Cl, Br, I, -CN, -CHO, $(CF_2)_rCF_3$, $(CH_2)_rOR^2$, NR^2R^{2a} , $C(O)R^{2c}$, $OC(O)R^2$, $(CF_2)_rCO_2R^{2a}$, $S(O)_pR^{2b}$, $NR^2(CH_2)_rOR^2$, $C(=NR^{2c})NR^2R^{2a}$, $NR^2C(O)R^{2b}$, $NR^2C(O)NHR^{2b}$, $NR^2C(O)_2R^{2a}$, $OC(O)NR^{2a}R^{2b}$, $C(O)NR^2R^{2a}$, $C(O)NR^2(CH_2)_rOR^2$, $SO_2NR^2R^{2a}$, $NR^2SO_2R^{2b}$, C_{3-6} carbocycle substituted with 0-2 R^{4a} , and 5-10 membered heterocycle consisting of carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ substituted with 0-2 R^{4a} , provided that R^{1b} forms other than an N-halo, N-N, N-S, N-O, or N-CN bond;

R^{1c} is selected from H, $CH(CH_2OR^2)_2$, $C(O)R^{2c}$, $C(O)NR^2R^{2a}$, $S(O)R^{2b}$, $S(O)_2R^{2b}$, and $SO_2NR^2R^{2a}$;

R^{1d} is selected from C_{3-13} carbocycle substituted with 0-2 R^{4a} , and 5-13 membered heterocycle consisting of carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ substituted with 0-2 R^{4a} , provided that R^{1d} forms other than an N-N, N-S, or N-O bond;

R^2 , at each occurrence, is selected from H, CF_3 , C_{1-6} alkyl, benzyl, C_{3-6} carbocyclic residue substituted with 0-2 R^{4b} , and 5-6 membered heterocyclic system comprising carbon atoms and from 1-4 heteroatoms selected from the

group consisting of N, O, and S substituted with 0-2 R^{4b};

5 R^{2a}, at each occurrence, is selected from H, CF₃, C₁₋₆ alkyl, benzyl, phenethyl, C₃₋₆ carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system comprising carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

10 R^{2b}, at each occurrence, is selected from CF₃, C₁₋₄ alkoxy, C₁₋₆ alkyl, benzyl, C₃₋₆ carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system comprising carbon atoms and from 1-4 heteroatoms
15 selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

R^{2c}, at each occurrence, is selected from CF₃, OH, C₁₋₄ alkoxy, C₁₋₆ alkyl, benzyl, C₃₋₆ carbocyclic residue
20 substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system comprising carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

25 alternatively, R² and R^{2a}, together with the atom to which they are attached, combine to form a 5 or 6 membered saturated, partially saturated or unsaturated ring substituted with 0-2 R^{4b} and comprising carbon atoms and from 0-1 additional heteroatoms selected from the group
30 consisting of N, O, and S;

R³, at each occurrence, is selected from H, C₁₋₄ alkyl, and phenyl;

R^{3a}, at each occurrence, is selected from H, C₁₋₄ alkyl, and phenyl;

5 R^{3b}, at each occurrence, is selected from H, C₁₋₄ alkyl, and phenyl;

R^{3c}, at each occurrence, is selected from C₁₋₄ alkyl, and phenyl;

10 R^{3d}, at each occurrence, is selected from H, C₁₋₄ alkyl, C₁₋₄ alkyl-phenyl, and C(=O)R^{3c};

A is selected from:

15 C₃₋₁₀ carbocyclic residue substituted with 0-2 R⁴, and 5-12 membered heterocyclic system comprising carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R⁴;

20 B is selected from: H, Y, and X-Y, provided that Z and B are attached to different atoms on A;

X is selected from -(CR²R^{2a})₁₋₄-, -CR²(CR²R^{2b})(CH₂)_t-, -C(O)-, -C(=NR^{1c})-, -CR²(NR^{1c}R²)-, -CR²(OR²)-, -CR²(SR²)-, -C(O)CR²R^{2a}-, -CR²R^{2a}C(O)-, -S-, -S(O)-, -S(O)₂-, -SCR²R^{2a}-, -S(O)CR²R^{2a}-, -S(O)₂CR²R^{2a}-, -CR²R^{2a}S-, -CR²R^{2a}S(O)-, -CR²R^{2a}S(O)₂-, -S(O)₂NR²-, -NR²S(O)₂-, -NR²S(O)₂CR²R^{2a}-, -CR²R^{2a}S(O)₂NR²-, -NR²S(O)₂NR²-, -C(O)NR²-, -NR²C(O)-, -C(O)NR²CR²R^{2a}-, -NR²C(O)CR²R^{2a}-, -CR²R^{2a}C(O)NR²-, -CR²R^{2a}NR²C(O)-, -NR²C(O)O-, -OC(O)NR²-, -NR²C(O)NR²-, -NR²-, -NR²CR²R^{2a}-, -CR²R^{2a}NR²-, O, -CR²R^{2a}O-, and -OCR²R^{2a}-;

25

30

Y is selected from:

C₃₋₁₀ carbocyclic residue substituted with 0-2 R^{4a}, and
 5-12 membered heterocyclic system comprising carbon
 atoms and from 1-4 heteroatoms selected from the group
 consisting of N, O, and S substituted with 0-2 R^{4a};

5

R⁴, at each occurrence, is selected from H, =O, (CH₂)_rOR²,
 (CH₂)_rF, (CH₂)_rCl, (CH₂)_rBr, (CH₂)_rI, C₁₋₄ alkyl,
 (CH₂)_rCN, (CH₂)_rNO₂, (CH₂)_rNR²R^{2a}, C(O)R^{2c}, NR²C(O)R^{2b},
 C(O)NR²R^{2a}, NR²C(O)NR²R^{2a}, C(=NR²)NR²R^{2a},
 10 C(=NS(O)₂R⁵)NR²R^{2a}, NHC(=NR²)NR²R^{2a}, C(O)NHC(=NR²)NR²R^{2a},
 SO₂NR²R^{2a}, NR²SO₂NR²R^{2a}, NR²SO₂-C₁₋₄ alkyl, NR²SO₂R⁵,
 S(O)_pR⁵, (CF₂)_rCF₃, (CH₂)_r-CF₃, NCH₂R^{1c}, OCH₂R^{1c}, SCH₂R^{1c},
 N(CH₂)₂(CH₂)_tR^{1b}, O(CH₂)₂(CH₂)_tR^{1b}, S(CH₂)₂(CH₂)_tR^{1b}, 5-6
 membered carbocycle substituted with 0-1 R⁵, and 5-6
 15 membered heterocycle consisting of: carbon atoms and
 1-4 heteroatoms selected from the group consisting of
 N, O, and S(O)_p substituted with 0-1 R⁵;

R^{4a}, at each occurrence, is selected from H, =O, (CH₂)_rOR²,
 20 (CF₂)_rCF₃, (CH₂)_r-CF₃, (CH₂)_r-F, (CH₂)_r-Br, (CH₂)_r-Cl,
 C₁₋₄ alkyl, (CH₂)_rCN, (CH₂)_rNO₂, (CH₂)_rNR²R^{2a},
 (CH₂)_rC(O)R^{2c}, NR²C(O)R^{2b}, C(O)NR²R^{2a}, (CH₂)_rN=CHOR³,
 C(O)NH(CH₂)₂NR²R^{2a}, NR²C(O)NR²R^{2a}, C(=NR²)NR²R^{2a},
 NHC(=NR²)NR²R^{2a}, SO₂NR²R^{2a}, NR²SO₂NR²R^{2a}, NR²SO₂-C₁₋₄
 25 alkyl, NR²SO₂R⁵, C(O)NHSO₂-C₁₋₄ alkyl, S(O)_pR⁵, 5-6
 membered carbocycle substituted with 0-1 R⁵, and 5-6
 membered heterocycle consisting of: carbon atoms and
 1-4 heteroatoms selected from the group consisting of
 N, O, and S(O)_p substituted with 0-1 R⁵;

30

R^{4b}, at each occurrence, is selected from H, =O, (CH₂)_rOR³,
 (CH₂)_r-F, (CH₂)_r-Cl, (CH₂)_r-Br, (CH₂)_r-I, C₁₋₄ alkyl,
 (CH₂)_r-CN, (CH₂)_r-NO₂, (CH₂)_rNR³R^{3a}, (CH₂)_rC(O)R³,

$(\text{CH}_2)_r\text{C}(\text{O})\text{OR}^{3c}$, $\text{NR}^3\text{C}(\text{O})\text{R}^{3a}$, $\text{C}(\text{O})\text{NR}^3\text{R}^{3a}$, $\text{NR}^3\text{C}(\text{O})\text{NR}^3\text{R}^{3a}$,
 $\text{C}(=\text{NR}^3)\text{NR}^3\text{R}^{3a}$, $\text{NR}^3\text{C}(=\text{NR}^3)\text{NR}^3\text{R}^{3a}$, $\text{SO}_2\text{NR}^3\text{R}^{3a}$, $\text{NR}^3\text{SO}_2\text{NR}^3\text{R}^{3a}$,
 $\text{NR}^3\text{SO}_2\text{-C}_{1-4}$ alkyl, $\text{NR}^3\text{SO}_2\text{CF}_3$, $\text{NR}^3\text{SO}_2\text{-phenyl}$, $\text{S}(\text{O})_p\text{CF}_3$,
 $\text{S}(\text{O})_p\text{-C}_{1-4}$ alkyl, $\text{S}(\text{O})_p\text{-phenyl}$, $(\text{CH}_2)_r\text{CF}_3$, and $(\text{CF}_2)_r\text{CF}_3$;

5

R^5 , at each occurrence, is selected from H, C_{1-6} alkyl, =O,
 $(\text{CH}_2)_r\text{OR}^3$, F, Cl, Br, I, -CN, NO_2 , $(\text{CH}_2)_r\text{NR}^3\text{R}^{3a}$,
 $(\text{CH}_2)_r\text{C}(\text{O})\text{R}^3$, $(\text{CH}_2)_r\text{C}(\text{O})\text{OR}^{3c}$, $\text{NR}^3\text{C}(\text{O})\text{R}^{3a}$, $\text{C}(\text{O})\text{NR}^3\text{R}^{3a}$,
 $\text{NR}^3\text{C}(\text{O})\text{NR}^3\text{R}^{3a}$, $\text{CH}(=\text{NOR}^{3d})$, $\text{C}(=\text{NR}^3)\text{NR}^3\text{R}^{3a}$,
10 $\text{NR}^3\text{C}(=\text{NR}^3)\text{NR}^3\text{R}^{3a}$, $\text{SO}_2\text{NR}^3\text{R}^{3a}$, $\text{NR}^3\text{SO}_2\text{NR}^3\text{R}^{3a}$, $\text{NR}^3\text{SO}_2\text{-C}_{1-4}$
alkyl, $\text{NR}^3\text{SO}_2\text{CF}_3$, $\text{NR}^3\text{SO}_2\text{-phenyl}$, $\text{S}(\text{O})_p\text{CF}_3$, $\text{S}(\text{O})_p\text{-C}_{1-4}$
alkyl, $\text{S}(\text{O})_p\text{-phenyl}$, $(\text{CF}_2)_r\text{CF}_3$, phenyl substituted with
0-2 R^6 , naphthyl substituted with 0-2 R^6 , and benzyl
substituted with 0-2 R^6 ;

15

R^6 , at each occurrence, is selected from H, OH, $(\text{CH}_2)_r\text{OR}^2$,
halo, C_{1-4} alkyl, CN, NO_2 , $(\text{CH}_2)_r\text{NR}^2\text{R}^{2a}$, $(\text{CH}_2)_r\text{C}(\text{O})\text{R}^{2b}$,
 $\text{NR}^2\text{C}(\text{O})\text{R}^{2b}$, $\text{NR}^2\text{C}(\text{O})\text{NR}^2\text{R}^{2a}$, $\text{C}(=\text{NH})\text{NH}_2$, $\text{NHC}(=\text{NH})\text{NH}_2$,
 $\text{SO}_2\text{NR}^2\text{R}^{2a}$, $\text{NR}^2\text{SO}_2\text{NR}^2\text{R}^{2a}$, and $\text{NR}^2\text{SO}_2\text{C}_{1-4}$ alkyl;

20

R^7 , at each occurrence, is selected from H, OH, C_{1-4}
alkoxycarbonyl, C_{6-10} aryloxy, C_{6-10} aryloxycarbonyl,
 C_{6-10} arylmethylcarbonyl, C_{1-4} alkylcarbonyloxy C_{1-4}
alkoxycarbonyl, C_{6-10} arylcarbonyloxy C_{1-4}
25 alkoxycarbonyl, C_{1-6} alkylaminocarbonyl,
phenylaminocarbonyl, and phenyl C_{1-4} alkoxycarbonyl;

R^8 , at each occurrence, is selected from H, C_{1-6} alkyl, and
 $(\text{CH}_2)_n\text{-phenyl}$;

30

alternatively, R^7 and R^8 , when attached to the same nitrogen,
combine to form a 5-6 membered heterocyclic ring

consisting of carbon atoms and 0-2 additional heteroatoms selected from the group consisting of N, O, and S(O)_p;

5 R⁹, at each occurrence, is selected from H, C₁₋₆ alkyl, and (CH₂)_n-phenyl;

n, at each occurrence, is selected from 0, 1, 2, and 3;

10 m, at each occurrence, is selected from 0, 1, and 2;

p, at each occurrence, is selected from 0, 1, and 2;

r, at each occurrence, is selected from 0, 1, 2, and 3;

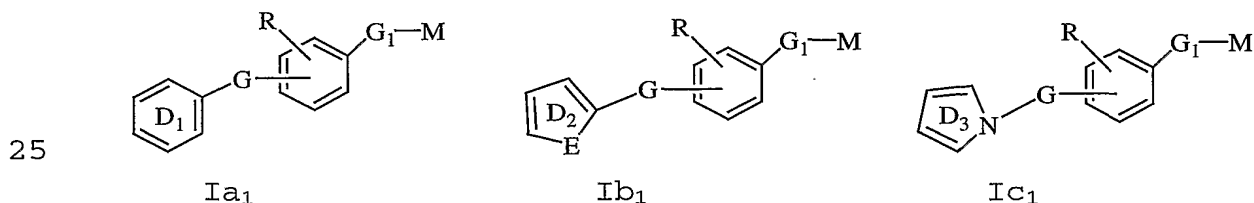
15

s, at each occurrence, is selected from 0, 1, and 2; and,

t, at each occurrence, is selected from 0, 1, 2, and 3.

20

[2] In a preferred embodiment, the present invention provides a novel compound, wherein the compound is of formula Ia₁-Ic₁, wherein:



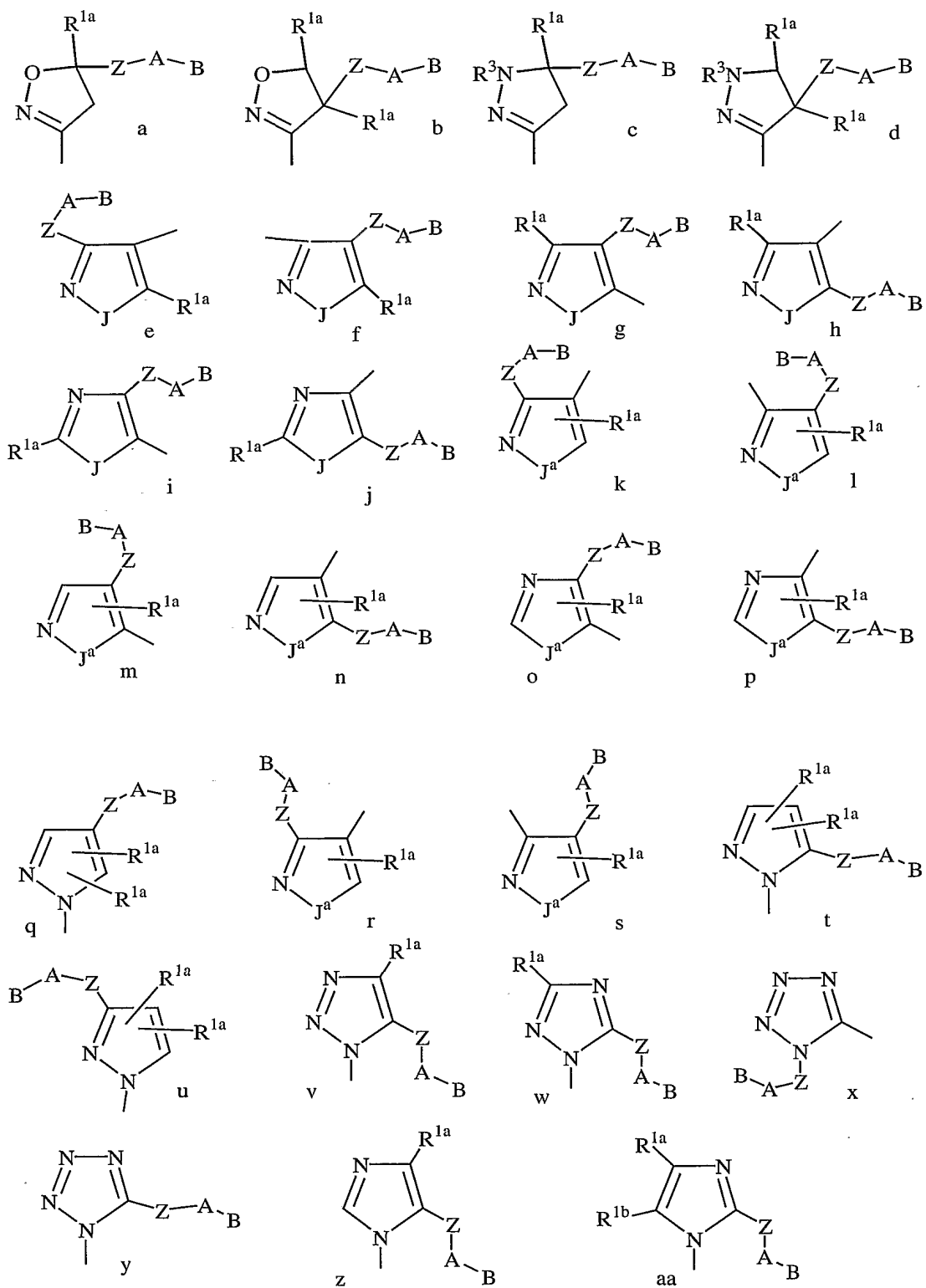
ring D₂ is a 5-membered heteroaromatic ring system comprising E, carbon atoms, and 0-2 N atoms, wherein E is selected from O, S, and N-R^C and ring D₂ is substituted with 1 R^a and 0-1 R^b;

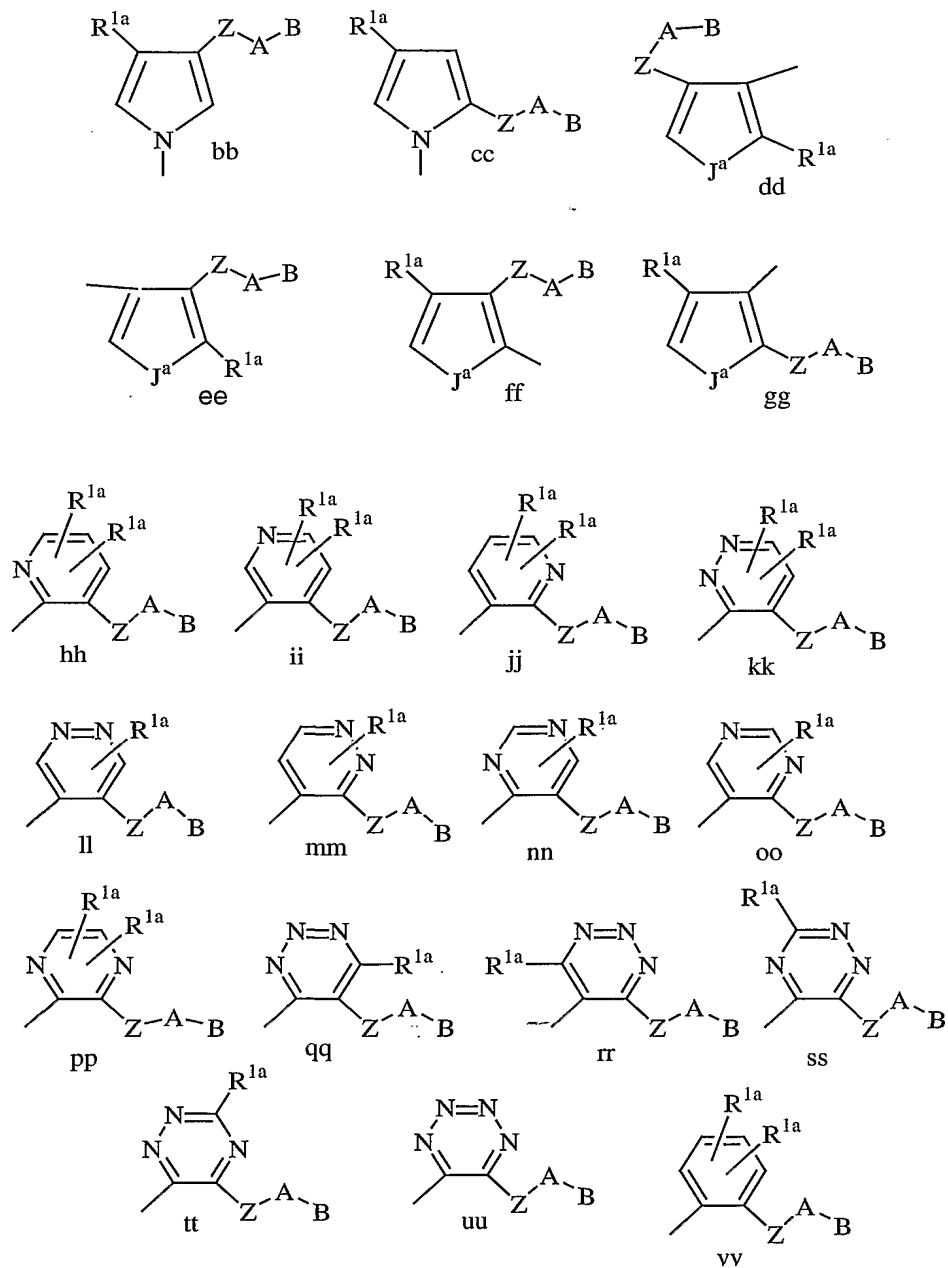
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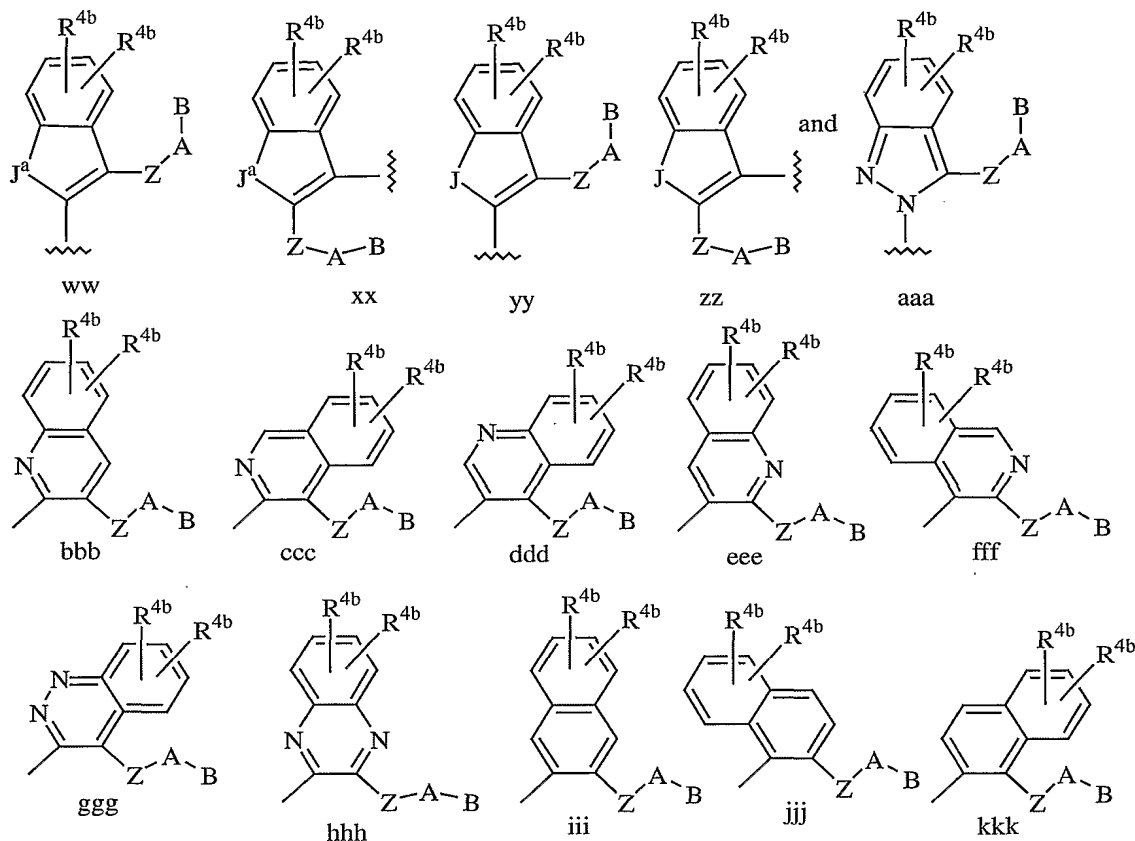
ring D₃ is a 5-membered heteroaromatic ring system comprising carbon atoms and from 0-3 additional N atoms and ring D₃ is substituted with 1 R^a and 0-1 R^b;

- 5 R is selected from H, Cl, F, Br, I, OH, C₁₋₃ alkoxy, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), CH₂N(C₁₋₃ alkyl)₂, CH₂CH₂NH₂, CH₂CH₂NH(C₁₋₃ alkyl), and CH₂CH₂N(C₁₋₃ alkyl)₂;
- 10 R^a is selected from H, OH, SH, C₁₋₃ alkoxy, C₁₋₃ thioalkoxy, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), CH₂N(C₁₋₃ alkyl)₂, CH₂CH₂NH₂, CH₂CH₂NH(C₁₋₃ alkyl), and CH₂CH₂N(C₁₋₃ alkyl)₂;
- 15 R^b is selected from H, C₁₋₄ alkyl, Cl, F, Br, I, OH, C₁₋₃ alkoxy, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), CH₂N(C₁₋₃ alkyl)₂, CH₂CH₂NH₂, CH₂CH₂NH(C₁₋₃ alkyl), and CH₂CH₂N(C₁₋₃ alkyl)₂;
- 20 R^c is selected from H, C₁₋₄ alkyl, C₁₋₃ alkoxy, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), CH₂N(C₁₋₃ alkyl)₂, CH₂CH₂NH₂, CH₂CH₂NH(C₁₋₃ alkyl), and CH₂CH₂N(C₁₋₃ alkyl)₂;
- 25 G₁ is absent or is selected from CH₂, C(O), O, NR³, S(O)_p, CH₂CH₂, C(O)CH₂, CH₂C(O), OCH₂, CH₂O, NR³CH₂, CH₂NR³, S(O)_pCH₂, CH₂S(O)_p, CH₂CH₂CH₂, C(O)CH₂CH₂, CH₂C(O)CH₂, CH₂CH₂C(O), OCH₂CH₂, CH₂OCH₂, CH₂CH₂O, NR³CH₂CH₂, CH₂NR³CH₂, CH₂CH₂NR³, S(O)_pCH₂CH₂, CH₂S(O)_pCH₂, and CH₂CH₂S(O)_p, and
 30 provided that G₁-M form other than a N-N, O-N, or S-N bond;

M is selected from the group:







J is O or S;

5 J^a is NH or NR^{1a};

G₁ is absent or is selected from (CR³R^{3a})₁₋₃,

(CR³R^{3a})_uC(O)(CR³R^{3a})_w, (CR³R^{3a})_uO(CR³R^{3a})_w,

(CR³R^{3a})_uNR³(CR³R^{3a})_w, (CR³R^{3a})_uC(O)NR³(CR³R^{3a})_w,

10 (CR³R^{3a})_uNR³C(O)(CR³R^{3a})_w, (CR³R^{3a})_uS(CR³R^{3a})_w,

(CR³R^{3a})_uS(O)(CR³R^{3a})_w, (CR³R^{3a})_uS(O)₂(CR³R^{3a})_w,

(CR³R^{3a})_uS(O)NR³(CR³R^{3a})_w, and (CR³R^{3a})_uS(O)₂NR³(CR³R^{3a})_w,

wherein u + w total 0, 1, or 2, provided that G₁ does not form a N-N, N-O, N-S, NCH₂N, NCH₂O, or NCH₂S bond

15 with either group to which it is attached;

A is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R⁴;

phenyl, piperidinyl, piperazinyl, pyridyl,
 pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl,
 pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl,
 isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl,
 5 thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl,
 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl,
 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl,
 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl,
 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl,
 10 1,2,5-triazolyl, 1,3,4-triazolyl, benzofuranyl,
 benzothiofuranyl, indolyl, benzimidazolyl,
 benzoxazolyl, benzthiazolyl, indazolyl, benzisoxazolyl,
 benzisothiazolyl, and isoindazolyl;

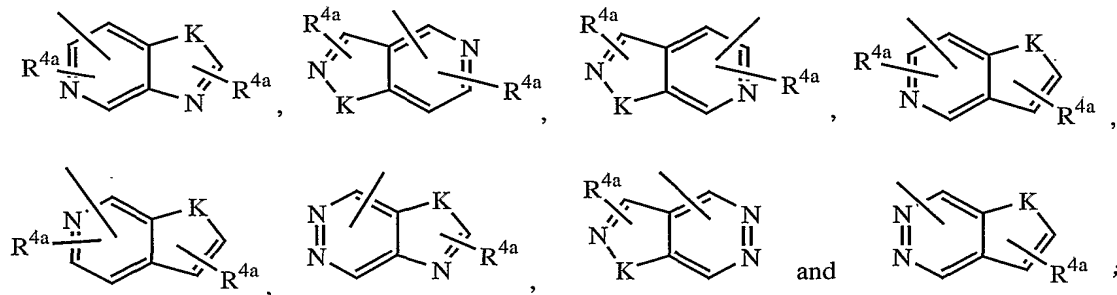
15 X is selected from $-(CR^2R^{2a})_{1-4}-$, $-C(O)-$, $-C(=NR^{1c})-$,
 $-CR^2(NR^{1c}R^2)-$, $-C(O)CR^2R^{2a}-$, $-CR^2R^{2a}C(O)-$, $-C(O)NR^2-$,
 $-NR^2C(O)-$, $-C(O)NR^2CR^2R^{2a}-$, $-NR^2C(O)CR^2R^{2a}-$,
 $-CR^2R^{2a}C(O)NR^2-$, $-CR^2R^{2a}NR^2C(O)-$, $-NR^2C(O)NR^2-$, $-NR^2-$,
 $-NR^2CR^2R^{2a}-$, $-CR^2R^{2a}NR^2-$, O, $-CR^2R^{2a}O-$, and $-OCR^2R^{2a}-$;

20 Y is selected from one of the following carbocyclic and
 heterocyclic systems that are substituted with 0-2 R^{4a} ;
 cyclopropyl, cyclopentyl, cyclohexyl, phenyl,
 piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl,
 25 morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl,
 oxazolyl, isoxazolyl, isoxazoliny, thiazolyl,
 isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl,
 thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl,
 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl,
 30 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl,
 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl,
 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl,
 1,2,5-triazolyl, 1,3,4-triazolyl, benzofuranyl,
 benzothiofuranyl, indolyl, benzimidazolyl,

benzoxazolyl, benzthiazolyl, indazolyl, benzisoxazolyl, benzisothiazolyl, and isoindazolyl;

alternatively, Y is selected from the following bicyclic heteroaryl ring systems:

5



K is selected from O, S, NH, and N;

10 Z is selected from a bond, CH₂O, OCH₂, NH, CH₂NH, NHCH₂, CH₂C(O), C(O)CH₂, C(O)NH, NHC(O), CH₂S(O)₂, S(O)₂(CH₂), SO₂NH, and NHSO₂, provided that Z does not form a N-N, N-O, N-S, NCH₂N, NCH₂O, or NCH₂S bond with either group to which it is attached;

15

R⁴, at each occurrence, is selected from H, =O, (CH₂)_rOR², F, Cl, Br, I, C₁₋₄ alkyl, CN, NO₂, (CH₂)_rNR²R^{2a}, C(O)R^{2c}, NR²C(O)R^{2b}, C(O)NR²R^{2a}, NR²C(O)NR²R^{2a}, C(=NR²)NR²R^{2a}, SO₂NR²R^{2a}, NR²SO₂NR²R^{2a}, NR²SO₂-C₁₋₄ alkyl, NR²SO₂R⁵,
 20 S(O)_pR⁵, CF₃, NCH₂R^{1c}, OCH₂R^{1c}, SCH₂R^{1c}, N(CH₂)₂(CH₂)_tR^{1b}, O(CH₂)₂(CH₂)_tR^{1b}, S(CH₂)₂(CH₂)_tR^{1b}, 5-6 membered carbocycle substituted with 0-1 R⁵, and 5-6 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)_p substituted with 0-1 R⁵; and,

25

R^{4a}, at each occurrence, is selected from H, =O, (CH₂)_rOR², CF₃, F, Br, Cl, C₁₋₄ alkyl, CN, NO₂, (CH₂)_rNR²R^{2a},

$(CH_2)_rC(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $NR^2C(O)NR^2R^{2a}$,
 $C(=NR^2)NR^2R^{2a}$, $NHC(=NR^2)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$,
 $NR^2SO_2-C_{1-4}$ alkyl, $NR^2SO_2R^5$, $C(O)NHSO_2-C_{1-4}$ alkyl,
 $S(O)_pR^5$, 5-6 membered carbocycle substituted with 0-1
5 R^5 , and 5-6 membered heterocycle consisting of: carbon
atoms and 1-4 heteroatoms selected from the group
consisting of N, O, and $S(O)_p$ substituted with 0-1 R^5 .

10 [3] In another preferred embodiment, the present invention
provides a novel compound, wherein the compound is of
formula Ib₁ or Ic₁, wherein;

ring D₂ is a 5-membered heteroaromatic ring system
15 comprising E, carbon atoms, and 0-2 N atoms, wherein E
is selected from O, S, and N-R^c and ring D₂ is
substituted with 1 R^a and 0-1 R^b;

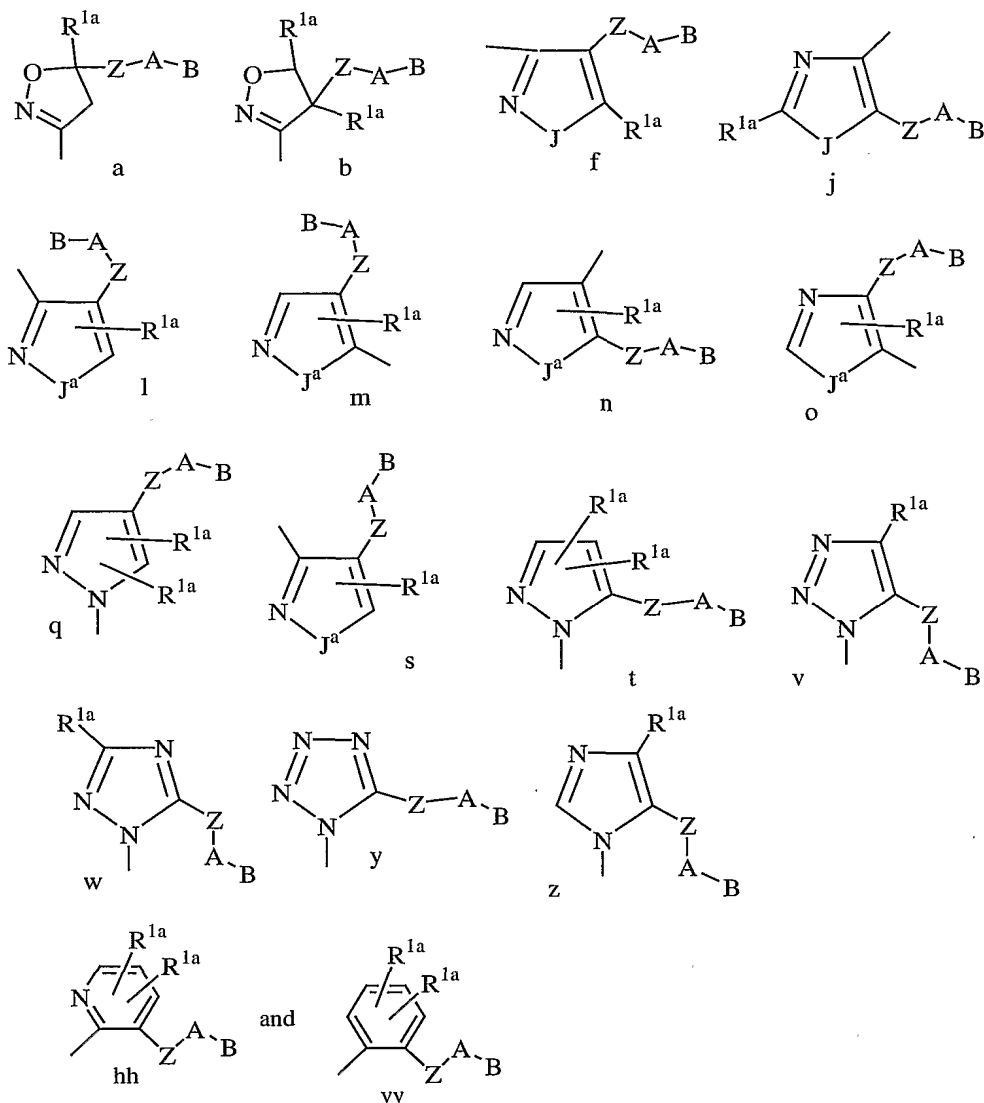
R is selected from H, Cl, F, Br, I, OH, C₁₋₃ alkoxy, NH₂,
20 NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, CH₂NH₂, CH₂NH(C₁₋₃
alkyl), and CH₂N(C₁₋₃ alkyl)₂;

R^a is selected from H, OH, SH, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃
alkyl)₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), and CH₂N(C₁₋₃
25 alkyl)₂;

R^b is selected from H, C₁₋₄ alkyl, Cl, F, Br, I, OH, C₁₋₃
alkoxy, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, CH₂NH₂,
CH₂NH(C₁₋₃ alkyl), and CH₂N(C₁₋₃ alkyl)₂;

30 R^c is selected from H, C₁₋₄ alkyl, C₁₋₃ alkoxy, NH₂, NH(C₁₋₃
alkyl), N(C₁₋₃ alkyl)₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), and
CH₂N(C₁₋₃ alkyl)₂;

M is selected from the group:



Y is selected from one of the following carbocyclic and
 5 heterocyclic systems which are substituted with 0-2 R^{4a} ;
 phenyl, piperidiny1, piperaziny1, pyridyl,
 pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl,
 pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl,
 isothiazolyl, pyrazolyl, imidazolyl, oxadiazole,
 10 thiadiazole, triazole, 1,2,3-oxadiazole, 1,2,4-
 oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 1,2,3-
 thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole,
 1,3,4-thiadiazole, 1,2,3-triazole, 1,2,4-triazole,

1,2,5-triazole, 1,3,4-triazole, benzofuran,
 benzothiofuran, indole, benzimidazole, benzimidazolone,
 benzoxazole, benzthiazole, indazole, benzisoxazole,
 benzisothiazole, and isoindazole;

5

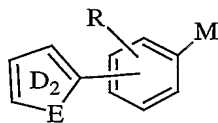
Z is selected from a bond, CH_2O , OCH_2 , NH , CH_2NH , NHCH_2 ,
 $\text{CH}_2\text{C}(\text{O})$, $\text{C}(\text{O})\text{CH}_2$, $\text{C}(\text{O})\text{NH}$, $\text{NHC}(\text{O})$, $\text{CH}_2\text{S}(\text{O})_2$, $\text{S}(\text{O})_2(\text{CH}_2)$,
 SO_2NH , and NHSO_2 , provided that Z does not form a N-N,
 N-O, N-S, NCH_2N , NCH_2O , or NCH_2S bond with either group
 10 to which it is attached;

R^4 , at each occurrence, is selected from H, $=\text{O}$, $(\text{CH}_2)_r\text{OR}^2$, F,
 Cl, Br, I, C_{1-4} alkyl, CN, NO_2 , $(\text{CH}_2)_r\text{NR}^2\text{R}^{2a}$, $\text{C}(\text{O})\text{R}^{2c}$,
 $\text{NR}^2\text{C}(\text{O})\text{R}^{2b}$, $\text{C}(\text{O})\text{NR}^2\text{R}^{2a}$, $\text{NR}^2\text{C}(\text{O})\text{NR}^2\text{R}^{2a}$, $\text{C}(=\text{NR}^2)\text{NR}^2\text{R}^{2a}$,
 15 $\text{SO}_2\text{NR}^2\text{R}^{2a}$, $\text{NR}^2\text{SO}_2\text{NR}^2\text{R}^{2a}$, $\text{NR}^2\text{SO}_2\text{-C}_{1-4}$ alkyl, $\text{NR}^2\text{SO}_2\text{R}^5$,
 $\text{S}(\text{O})_p\text{R}^5$, CF_3 , 5-6 membered carbocycle substituted with
 0-1 R^5 , and 5-6 membered heterocycle consisting of:
 carbon atoms and 1-4 heteroatoms selected from the
 group consisting of N, O, and $\text{S}(\text{O})_p$ substituted with 0-1
 20 R^5 ; and,

R^{4a} , at each occurrence, is selected from H, $=\text{O}$, $(\text{CH}_2)_r\text{OR}^2$,
 CF_3 , F, Br, Cl, C_{1-4} alkyl, CN, NO_2 , $(\text{CH}_2)_r\text{NR}^2\text{R}^{2a}$,
 $(\text{CH}_2)_r\text{C}(\text{O})\text{R}^{2c}$, $\text{NR}^2\text{C}(\text{O})\text{R}^{2b}$, $\text{C}(\text{O})\text{NR}^2\text{R}^{2a}$, $\text{NR}^2\text{C}(\text{O})\text{NR}^2\text{R}^{2a}$,
 25 $\text{C}(=\text{NR}^2)\text{NR}^2\text{R}^{2a}$, $\text{SO}_2\text{NR}^2\text{R}^{2a}$, $\text{C}(\text{O})\text{NHSO}_2\text{-C}_{1-4}$ alkyl, $\text{S}(\text{O})_p\text{R}^5$,
 5-6 membered carbocycle substituted with 0-1 R^5 , and 5-6
 membered heterocycle consisting of: carbon atoms and
 1-4 heteroatoms selected from the group consisting of
 N, O, and $\text{S}(\text{O})_p$ substituted with 0-1 R^5 .

30

[4] In another preferred embodiment, the present invention
 provides a novel compound, wherein the compound is of
 formula Ib_2 :

Ib₂

or a stereoisomer or pharmaceutically acceptable salt thereof, wherein;

5

ring D₂ is a 5-membered heteroaromatic ring system comprising E, carbon atoms, and 0-2 N atoms, wherein E is selected from O, S, and N-R^c and ring D₂ is substituted with 1 R^a and 0-1 R^b;

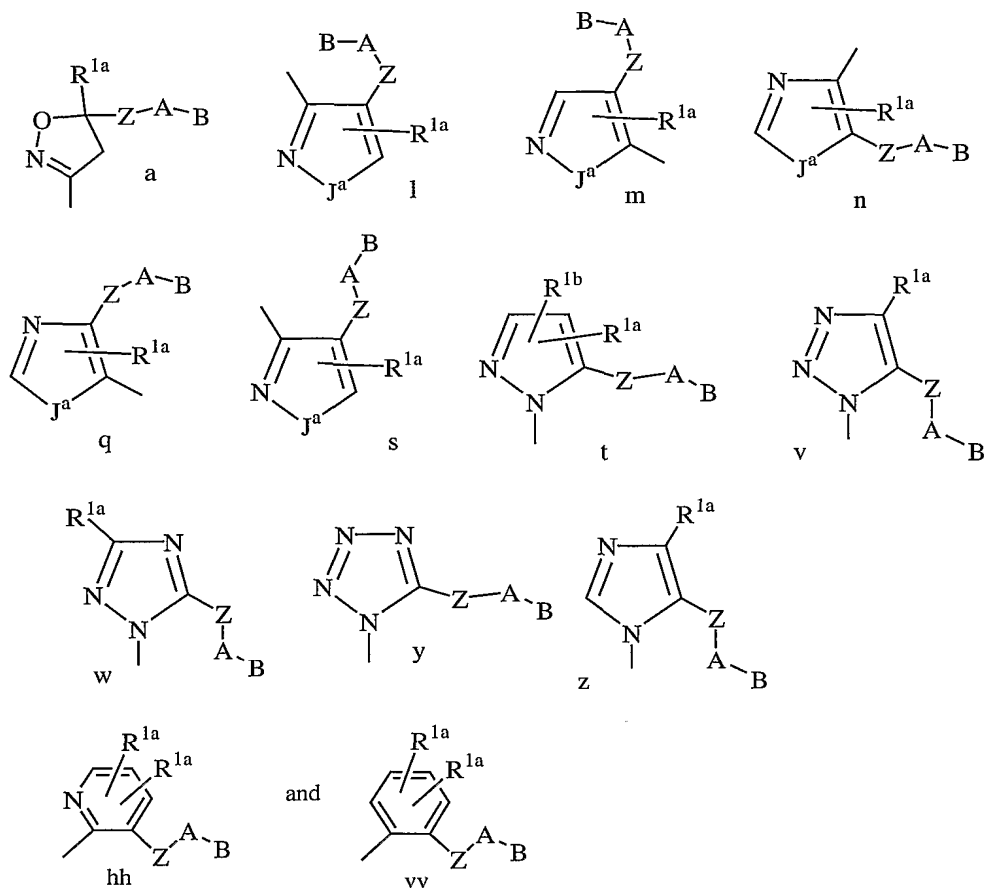
10

R is selected from H, Cl, F, Br, I, OH, C₁₋₃ alkoxy, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), and CH₂N(C₁₋₃ alkyl)₂;

15 R^a is selected from H, OH, SH, NH₂, NH(C₁₋₃ alkyl), and N(C₁₋₃ alkyl)₂;

R^b is selected from H, C₁₋₄ alkyl, Cl, F, Br, I, OH, C₁₋₃ alkoxy, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, CH₂NH₂,
20 CH₂NH(C₁₋₃ alkyl), and CH₂N(C₁₋₃ alkyl)₂;

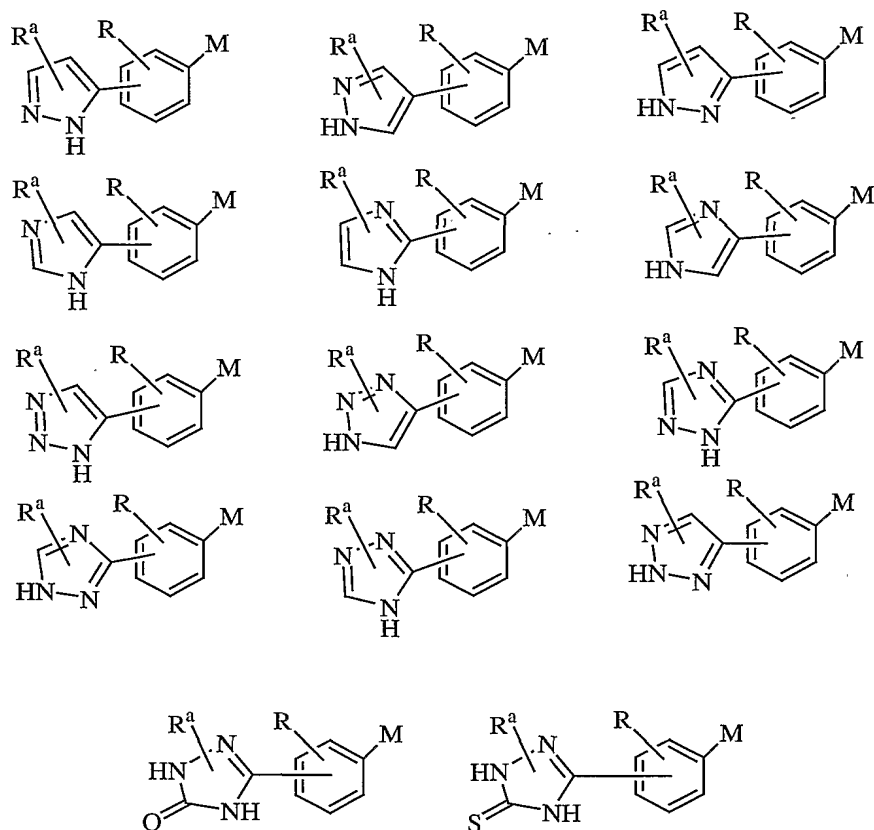
M is selected from the group:



G₁ is absent or is selected from CH₂, CH₂CH₂, CH₂O, OCH₂, NH, CH₂NH, NHCH₂, CH₂C(O), C(O)CH₂, C(O)NH, NHC(O),

5 CH₂S(O)₂, S(O)₂(CH₂), SO₂NH, and NHSO₂, provided that G₁ does not form a N-N, N-O, N-S, NCH₂N, NCH₂O, or NCH₂S bond with either group to which it is attached.

10 [5] In another preferred embodiment, the present invention provides a novel compound, wherein the compound is selected from one of the formulas:



5 or a stereoisomer or pharmaceutically acceptable salt thereof, wherein;

G_1 is absent;

10 A is selected from phenyl, piperidinyl, pyridyl, and pyrimidyl, and is substituted with 0-2 R^4 ; and,

B is selected from phenyl, pyrrolidino, N-pyrrolidino-carbonyl, morpholino, N-morpholino-carbonyl, 1,2,3-
 15 triazolyl, imidazolyl, and benzimidazolyl, and is substituted with 0-1 R^{4a} ;

R^2 , at each occurrence, is selected from H, CH_3 , CH_2CH_3 , cyclopropylmethyl, cyclobutyl, and cyclopentyl;

20

R^{2a}, at each occurrence, is selected from H, CH₃, and CH₂CH₃;

alternatively, R² and R^{2a}, together with the atom to which they are attached, combine to form pyrrolidine

5 substituted with 0-2 R^{4b} or piperidine substituted with 0-2 R^{4b};

R⁴, at each occurrence, is selected from OH, OR², (CH₂)OR², (CH₂)₂OR², F, Br, Cl, I, C₁₋₄ alkyl, NR²R^{2a}, (CH₂)NR²R^{2a},
10 (CH₂)₂NR²R^{2a}, CF₃, and (CF₂)CF₃;

R^{4a} is selected from C₁₋₄ alkyl, CF₃, OR², (CH₂)OR², (CH₂)₂OR², NR²R^{2a}, (CH₂)NR²R^{2a}, (CH₂)₂NR²R^{2a}, SR⁵, S(O)R⁵, S(O)₂R⁵, SO₂NR²R^{2a}, and 1-CF₃-tetrazol-2-yl;

15

R^{4b}, at each occurrence, is selected from H, CH₃, and OH;

R⁵, at each occurrence, is selected from CF₃, C₁₋₆ alkyl, phenyl, and benzyl; and,

20

r, at each occurrence, is selected from 0, 1, and 2.

[6] In another preferred embodiment, the present invention
25 provides a novel compound, wherein;

A is selected from the group: phenyl, piperidinyl, 2-pyridyl, 3-pyridyl, 2-pyrimidyl, 2-Cl-phenyl, 3-Cl-phenyl, 2-F-phenyl, 3-F-phenyl, 2-methylphenyl, 2-aminophenyl, and 2-methoxyphenyl; and,

30

B is selected from the group: 2-(aminosulfonyl)phenyl, 2-(methylaminosulfonyl)phenyl, 1-pyrrolidinocarbonyl, 2-(methylsulfonyl)phenyl, 2-(N,N-

dimethylaminomethyl)phenyl, 2-(N-methylaminomethyl)phenyl, 2-(N-ethyl-N-methylaminomethyl)phenyl, 2-(N-pyrrolidinylmethyl)phenyl, 1-methyl-2-imidazolyl, 2-methyl-1-imidazolyl, 2-(dimethylaminomethyl)-1-imidazolyl, 2-(methylaminomethyl)-1-imidazolyl, 2-(N-(cyclopropylmethyl)aminomethyl)phenyl, 2-(N-(cyclobutyl)aminomethyl)phenyl, 2-(N-(cyclopentyl)aminomethyl)phenyl, 2-(N-(4-hydroxypiperidinyl)methyl)phenyl, and 2-(N-(3-hydroxypyrrolidinyl)methyl)phenyl.

[7] In another preferred embodiment, the present invention provides a novel compound selected from the group:

1-[3-(1',3',4'-Triazol-2'-on-5'-yl)phenyl]-3-trifluoromethyl-5-[(2'-N,N-dimethylaminomethyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole;

1-[3-(1',3',4'-Triazol-2'-on-5'-yl)phenyl]-3-trifluoromethyl-5-[(2'-N-pyrrolidinylmethyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole;

1-[3-(1',3',4'-Triazol-2'-on-5'-yl)phenyl]-3-trifluoromethyl-5-[(3-fluoro-2'-N,N-dimethylaminomethyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole;

1-[3-(1',3',4'-Triazol-2'-on-5'-yl)phenyl]-3-trifluoromethyl-5-[(3-fluoro-2'-N-pyrrolidinylmethyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole;

1-[3-(1',3',4'-Triazol-2'-on-5'-yl)phenyl]-3-trifluoromethyl-5-[(2'-sulfonylmethyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole;

5 1-[3-(1',3',4'-Triazol-2'-on-5'-yl)phenyl]-3-trifluoromethyl-5-[(3-fluoro-2'-sulfonylmethyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole;

10 1-[3-(2'-Amino-1',3',4'-triazol-5'-yl)phenyl]-3-trifluoromethyl-5-[(3-fluoro-2'-sulfonylmethyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole;

15 1-[3-(2'-Amino-1',3',4'-triazol-5'-yl)phenyl]-3-trifluoromethyl-5-[(3-fluoro-2'-N,N-dimethylaminomethyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole;

20 1-[3-(2'-Amino-1',3',4'-triazol-5'-yl)phenyl]-3-trifluoromethyl-5-[(3-fluoro-2'-N-pyrrolidinylmethyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole;

25 1-[3-(2'-Amino-3',4'-thiadiazol-5'-yl)phenyl]-3-trifluoromethyl-5-[(3-fluoro-2'-sulfonylmethyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole;

30 1-[3-(2'-Amino-3',4'-thiadiazol-5'-yl)phenyl]-3-trifluoromethyl-5-[(3-fluoro-2'-N,N-dimethylaminomethyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole;

1-[3-(2'-Amino-3',4'-thiadiazol-5'-yl)phenyl]-3-trifluoromethyl-5-[(3-fluoro-2'-N-pyrrolidinylmethyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole;

1-[3-(1',3',4'-Triazol-2'-on-5'-yl)phenyl]-3-trifluoromethyl-5-[4-(2'-(N,N-dimethylamino)methylimidazol-1'-yl)-2-fluorophenyl]aminocarbonyl]pyrazole;

5

1-[3-(1',3',4'-Triazol-2'-on-5'-yl)phenyl]-3-trifluoromethyl-5-[4-(2'-methylimidazol-1'-yl)-2-fluorophenyl]aminocarbonyl]pyrazole;

10 1-[3-(Pyrid-3'-yl)phenyl]-3-trifluoromethyl-5-[(3-fluoro-2'-sulfonylmethyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole;

15 1-[3-(Pyrid-3'-yl)phenyl]-3-trifluoromethyl-5-[(3-fluoro-2'-N,N-dimethylaminomethyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole;

20 1-[3-(Pyrid-3'-yl)phenyl]-3-trifluoromethyl-5-[(3-fluoro-2'-N-pyrrolidinylmethyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole;

25 1-[3-(Pyrid-4'-yl)phenyl]-3-trifluoromethyl-5-[(3-fluoro-2'-N,N-dimethylaminomethyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole;

1-[3-(Pyrid-4'-yl)phenyl]-3-trifluoromethyl-5-[(3-fluoro-2'-N-pyrrolidinylmethyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole;

30 1-[3-(Pyrid-4'-yl)phenyl]-3-trifluoromethyl-5-[(3-fluoro-2'-sulfonylmethyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole;

1-[3-(5-Amino-1,3,4-oxadiazol-2-yl)phenyl]-N-{2'-
[(dimethylamino)methyl]-3-fluoro-1,1'-biphenyl-4-yl}-3-
(trifluoromethyl)-1H-pyrazole-5-carboxamide;

5 1-[3-(5-Amino-1,3,4-oxadiazol-2-yl)phenyl]-N-(3-fluoro-2'-
{[(3S)-3-hydroxy-1-pyrrolidinyl]methyl}-1,1'-biphenyl-
4-yl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide;
and,

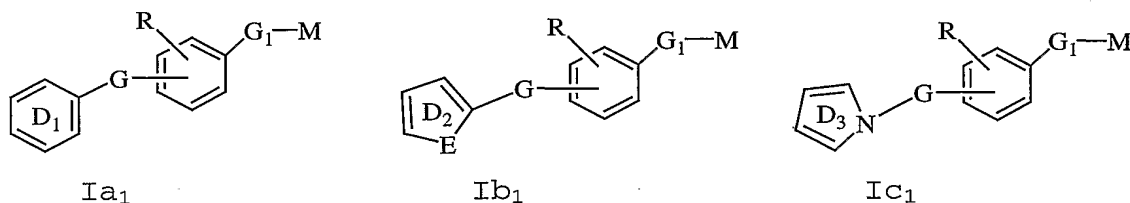
10 1-[3-(5-Amino-1,3,4-oxadiazol-2-yl)phenyl]-N-(3-fluoro-2'-
{[(3S)-3-hydroxy-1-pyrrolidinyl]methyl}-1,1'-biphenyl-
4-yl)-5-(trifluoromethyl)-1H-pyrazole-3-carboxamide;

or a pharmaceutically acceptable salt thereof.

15

In another embodiment, the present invention provides a
novel compound, wherein the compound is of formula Ia₁-Ic₁,
wherein:

20



ring D₂ is a 5-membered heteroaromatic ring system

25 comprising E, carbon atoms, and 0-2 N atoms, wherein E
is selected from O, S, and N-R^C and ring D₂ is
substituted with 1 R^a and 0-1 R^b;

ring D₃ is a 5-membered heteroaromatic ring system

30 comprising carbon atoms and from 0-3 additional N atoms
and ring D₃ is substituted with 1 R^a and 0-1 R^b;

R is selected from H, Cl, F, Br, I, OH, C₁₋₃ alkoxy, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), CH₂N(C₁₋₃ alkyl)₂, CH₂CH₂NH₂, CH₂CH₂NH(C₁₋₃ alkyl), and CH₂CH₂N(C₁₋₃ alkyl)₂;

5

R^a is selected from H, OH, SH, C₁₋₃ alkoxy, C₁₋₃ thioalkoxy, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), CH₂N(C₁₋₃ alkyl)₂, CH₂CH₂NH₂, CH₂CH₂NH(C₁₋₃ alkyl), and CH₂CH₂N(C₁₋₃ alkyl)₂;

10

R^b is selected from H, C₁₋₄ alkyl, Cl, F, Br, I, OH, C₁₋₃ alkoxy, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), CH₂N(C₁₋₃ alkyl)₂, CH₂CH₂NH₂, CH₂CH₂NH(C₁₋₃ alkyl), and CH₂CH₂N(C₁₋₃ alkyl)₂;

15

R^c is selected from H, C₁₋₄ alkyl, C₁₋₃ alkoxy, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), CH₂N(C₁₋₃ alkyl)₂, CH₂CH₂NH₂, CH₂CH₂NH(C₁₋₃ alkyl), and CH₂CH₂N(C₁₋₃ alkyl)₂; and,

20

G₁ is absent or is selected from CH₂, C(O), O, NR³, S(O)_p, CH₂CH₂, C(O)CH₂, CH₂C(O), OCH₂, CH₂O, NR³CH₂, CH₂NR³, S(O)_pCH₂, CH₂S(O)_p, CH₂CH₂CH₂, C(O)CH₂CH₂, CH₂C(O)CH₂, CH₂CH₂C(O), OCH₂CH₂, CH₂OCH₂, CH₂CH₂O, NR³CH₂CH₂, CH₂NR³CH₂, CH₂CH₂NR³, S(O)_pCH₂CH₂, CH₂S(O)_pCH₂, and CH₂CH₂S(O)_p, and provided that G₁-M form other than a N-N, O-N, or S-N bond.

25

30

In another embodiment, the present invention provides a novel compound, wherein the compound is of formula Ib₁ or Ic₁, wherein;

ring D₂ is a 5-membered heteroaromatic ring system comprising E, carbon atoms, and 0-2 N atoms, wherein E is selected from O, S, and N-R^C and ring D₂ is substituted with 1 R^a and 0-1 R^b;

5

R is selected from H, Cl, F, Br, I, OH, C₁₋₃ alkoxy, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), and CH₂N(C₁₋₃ alkyl)₂;

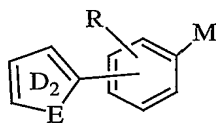
10 R^a is selected from H, OH, SH, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), and CH₂N(C₁₋₃ alkyl)₂;

15 R^b is selected from H, C₁₋₄ alkyl, Cl, F, Br, I, OH, C₁₋₃ alkoxy, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), and CH₂N(C₁₋₃ alkyl)₂; and,

R^C is selected from H, C₁₋₄ alkyl, C₁₋₃ alkoxy, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), and
20 CH₂N(C₁₋₃ alkyl)₂.

In another embodiment, the present invention provides a novel compound, wherein the compound is of formula Ib₂:

25

Ib₂

or a stereoisomer or pharmaceutically acceptable salt thereof, wherein;

30 ring D₂ is a 5-membered heteroaromatic ring system comprising E, carbon atoms, and 0-2 N atoms, wherein E

is selected from O, S, and N-R^C and ring D₂ is substituted with 1 R^a and 0-1 R^b;

R is selected from H, Cl, F, Br, I, OH, C₁₋₃ alkoxy, NH₂,
 5 NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), and CH₂N(C₁₋₃ alkyl)₂;

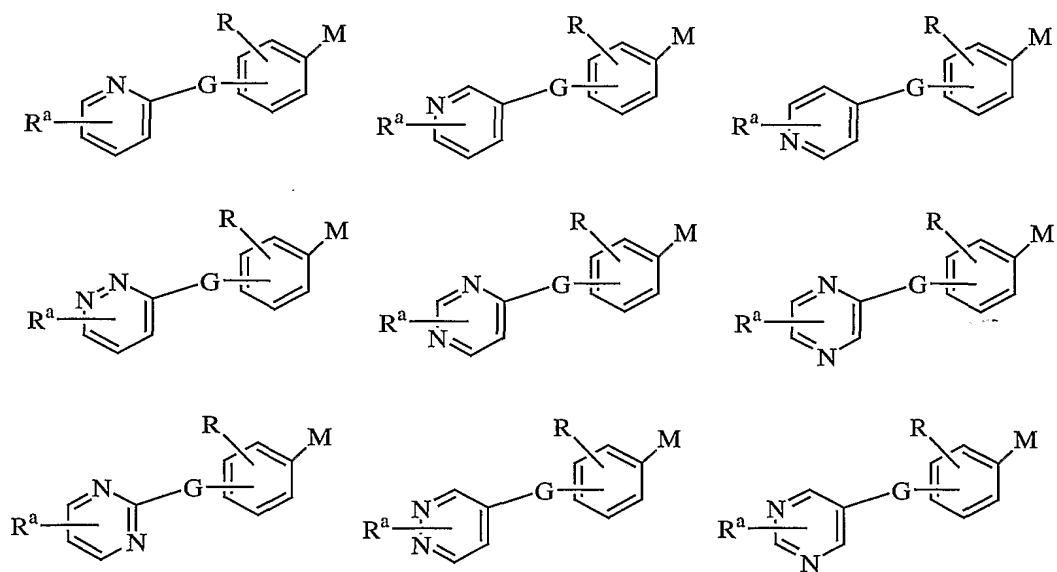
R^a is selected from H, OH, SH, NH₂, NH(C₁₋₃ alkyl), and N(C₁₋₃ alkyl)₂; and,

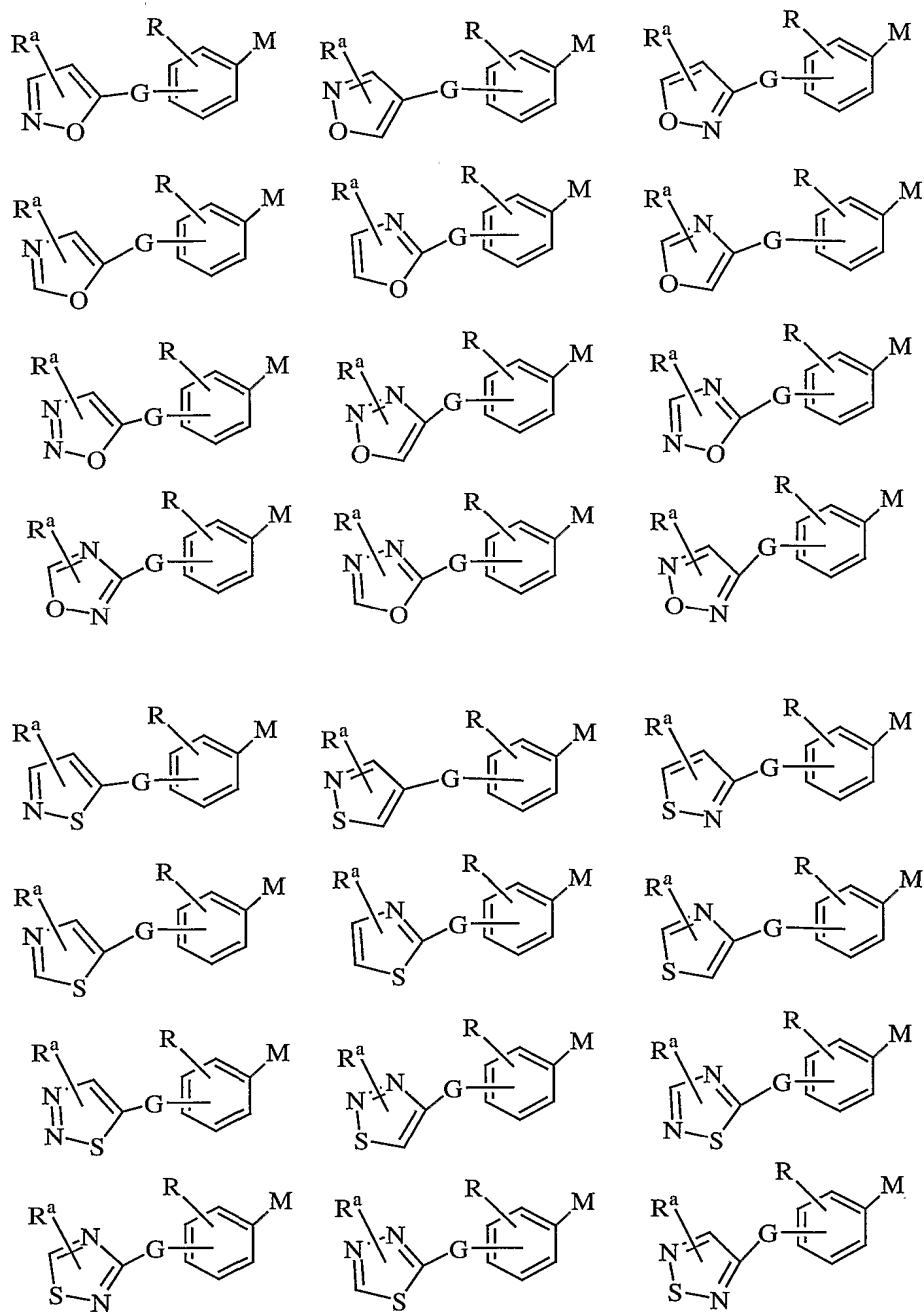
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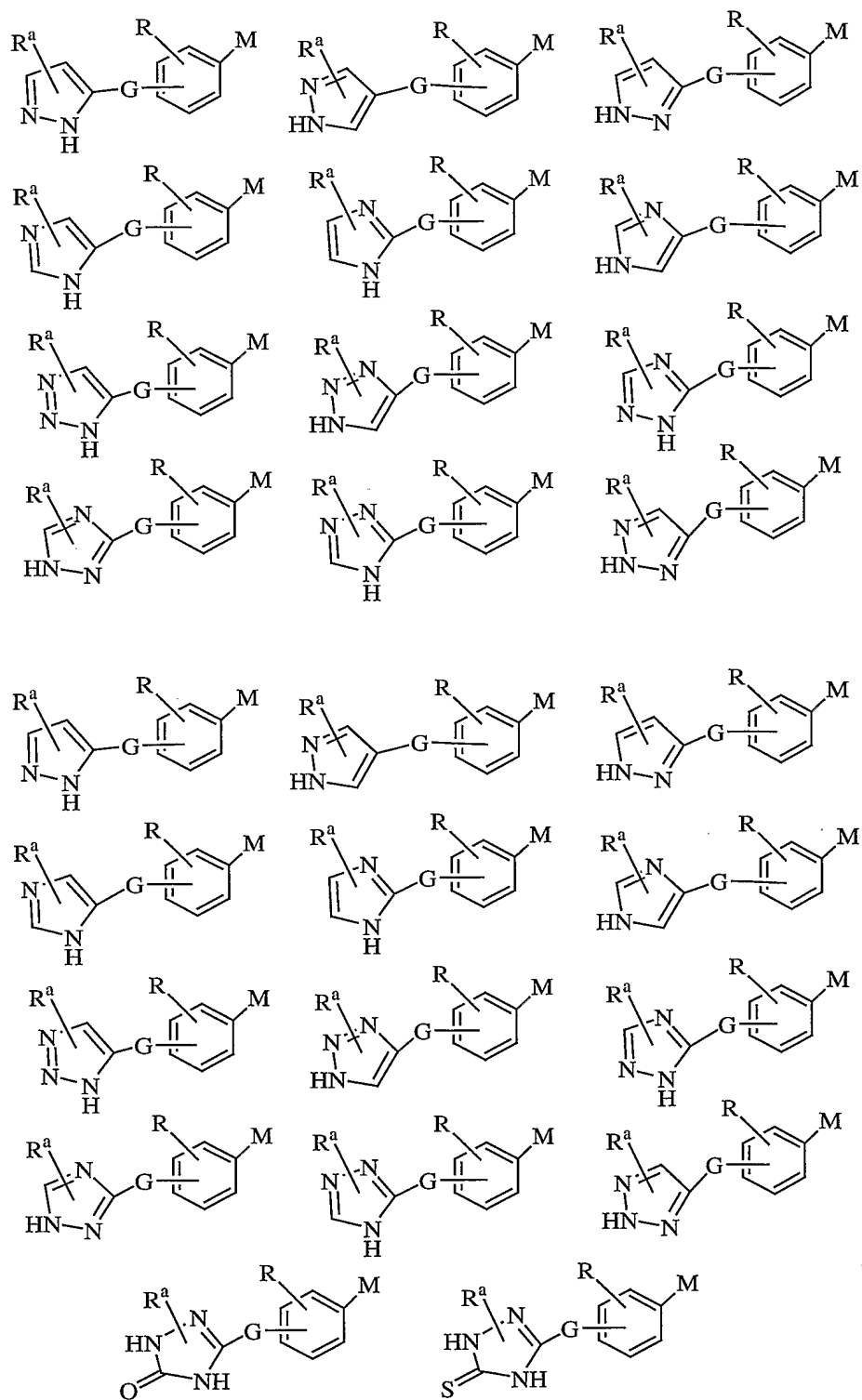
R^b is selected from H, C₁₋₄ alkyl, Cl, F, Br, I, OH, C₁₋₃ alkoxy, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), and CH₂N(C₁₋₃ alkyl)₂.

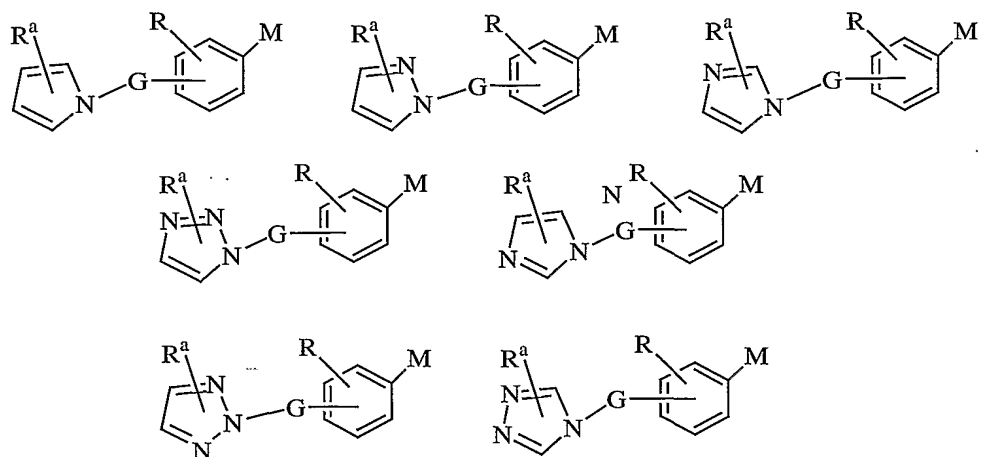
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In another embodiment, the present invention provides a novel compound selected from one of the formulas:





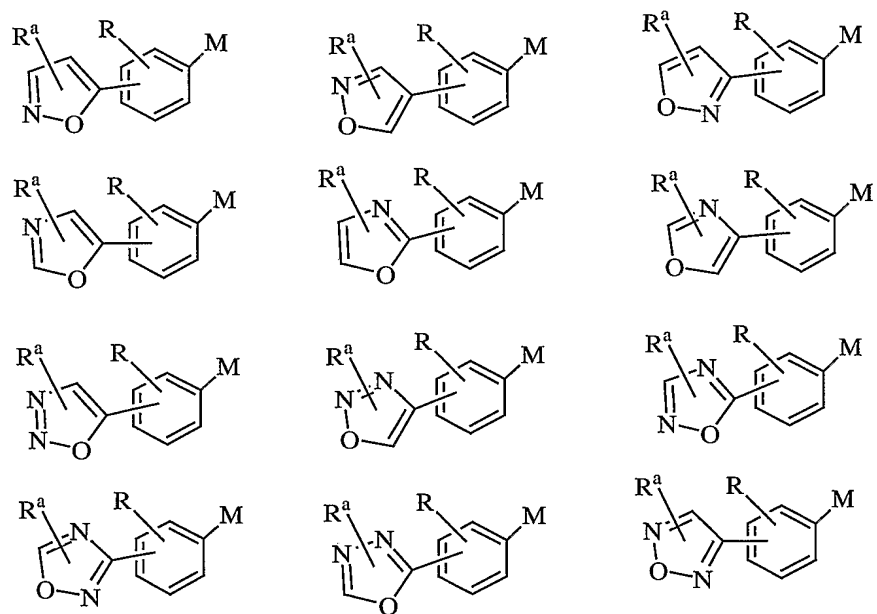




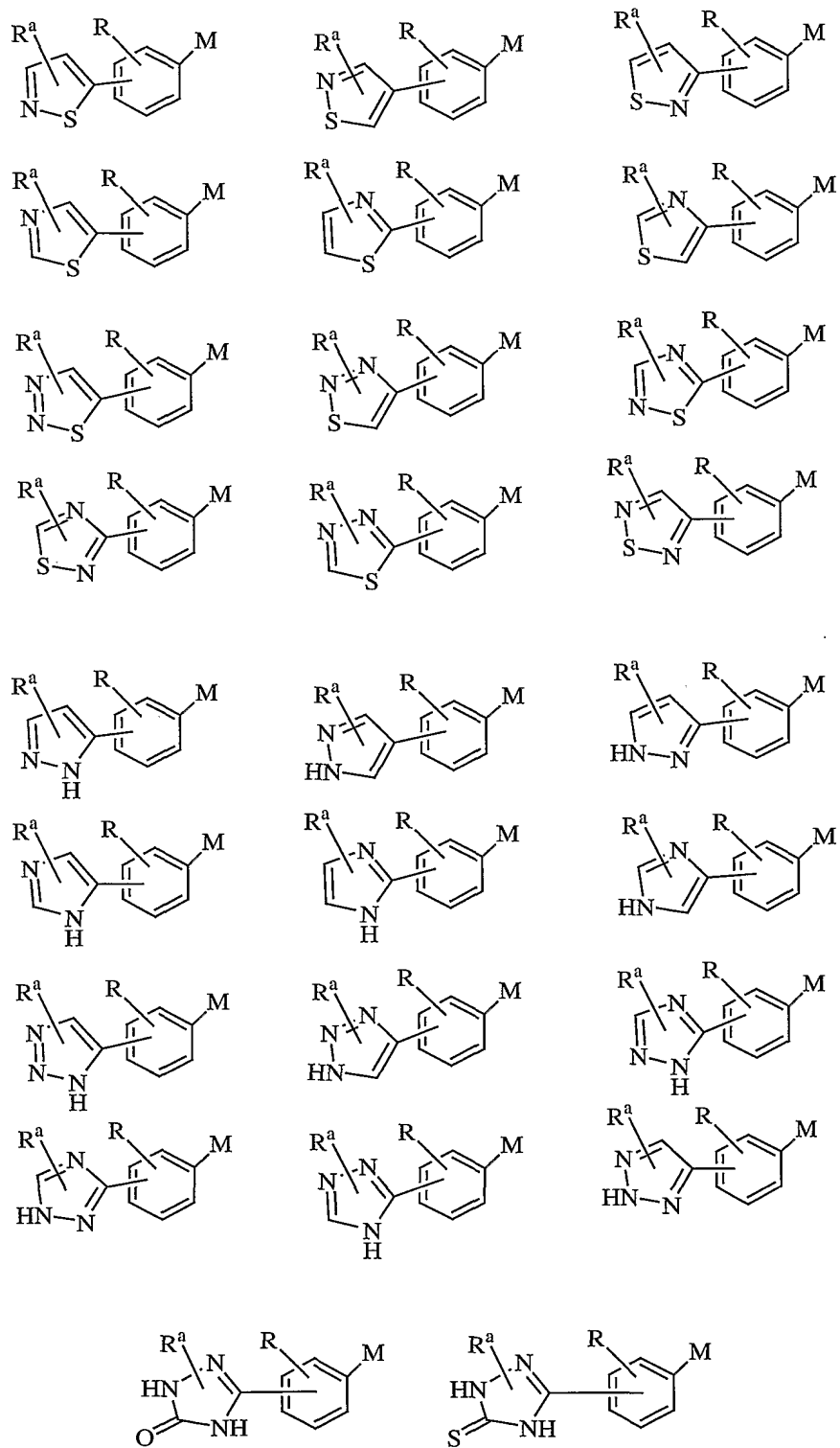
or a stereoisomer or pharmaceutically acceptable salt thereof.

5

In another embodiment, the present invention provides a novel compound selected from one of the formulas:



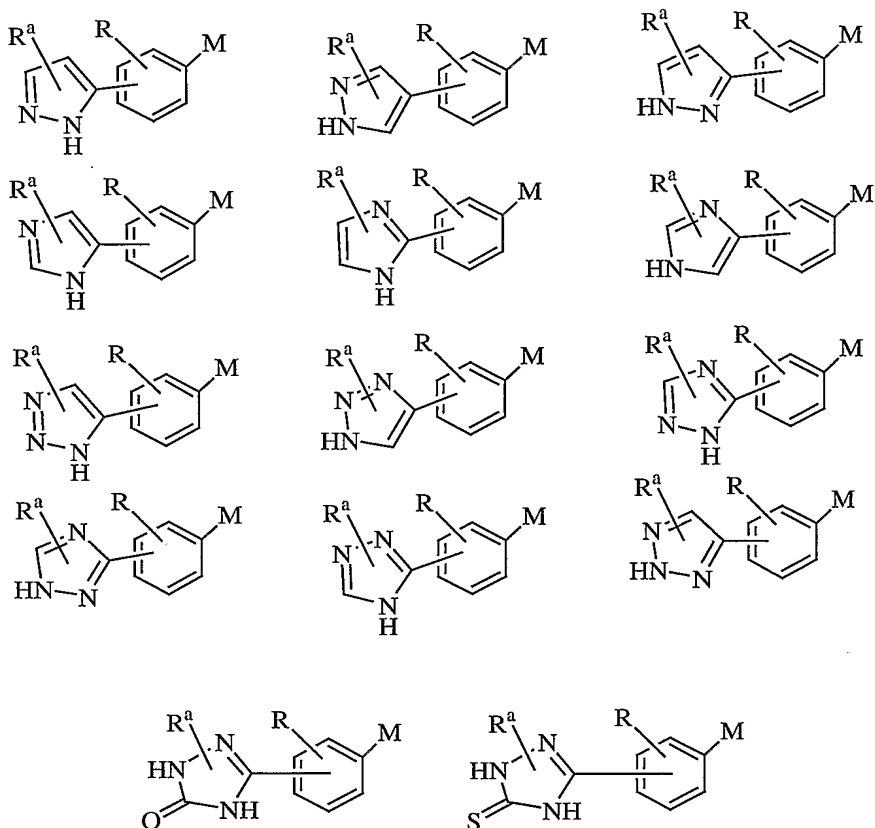
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5

or a stereoisomer or pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a novel compound selected from one of the formulas:



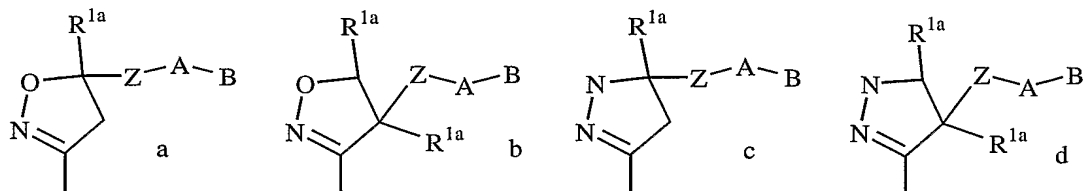
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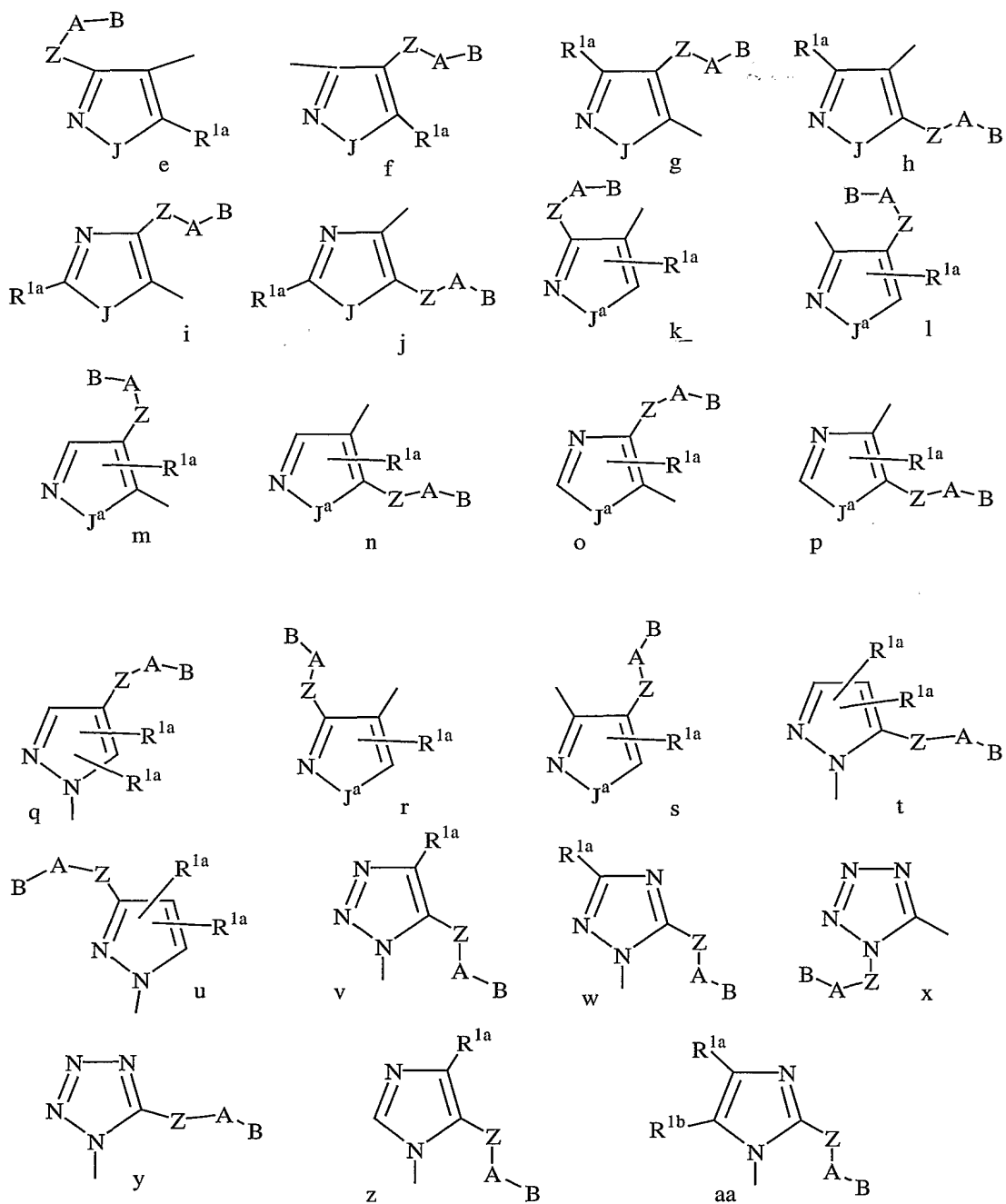
or a stereoisomer or pharmaceutically acceptable salt thereof.

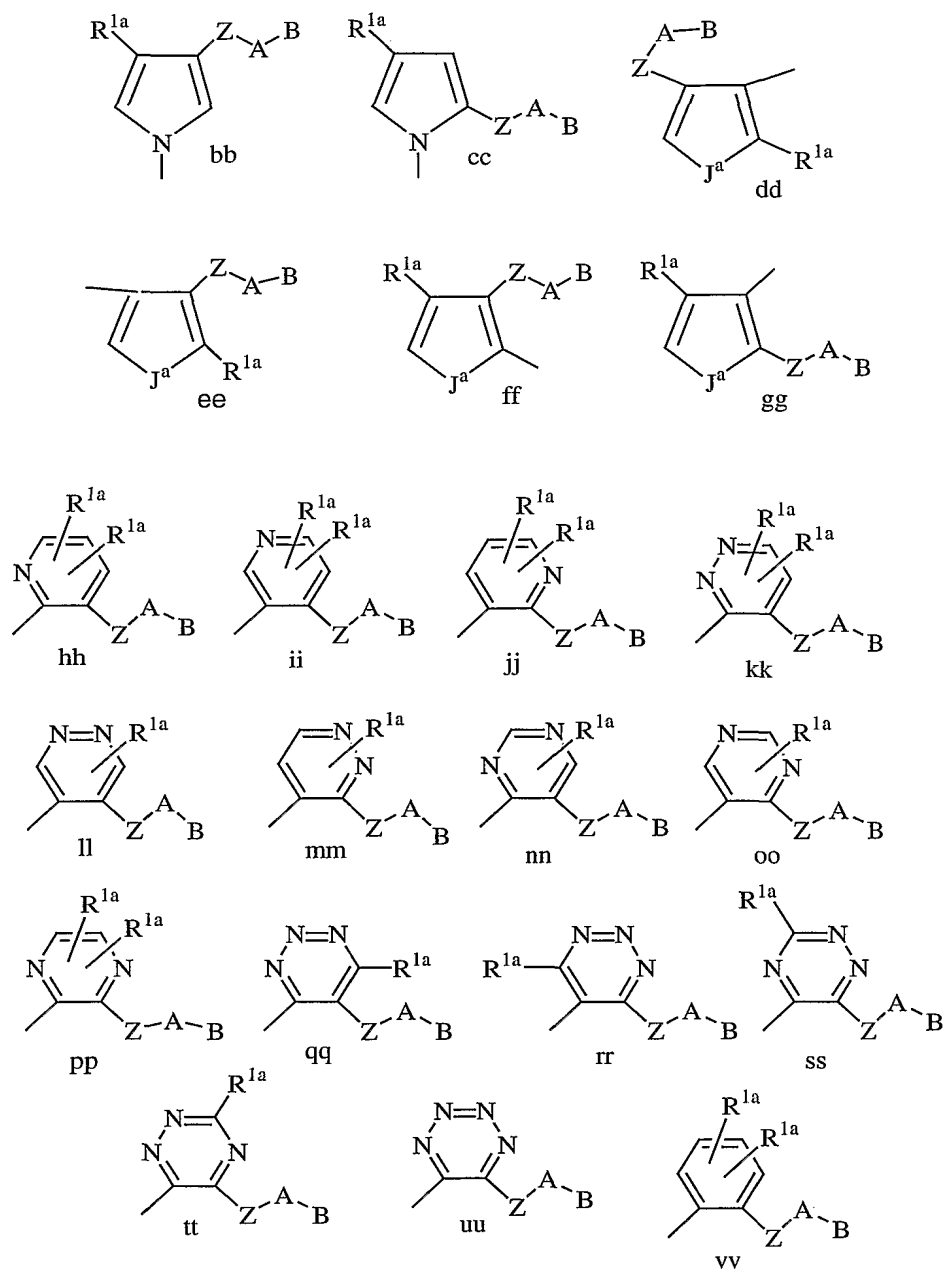
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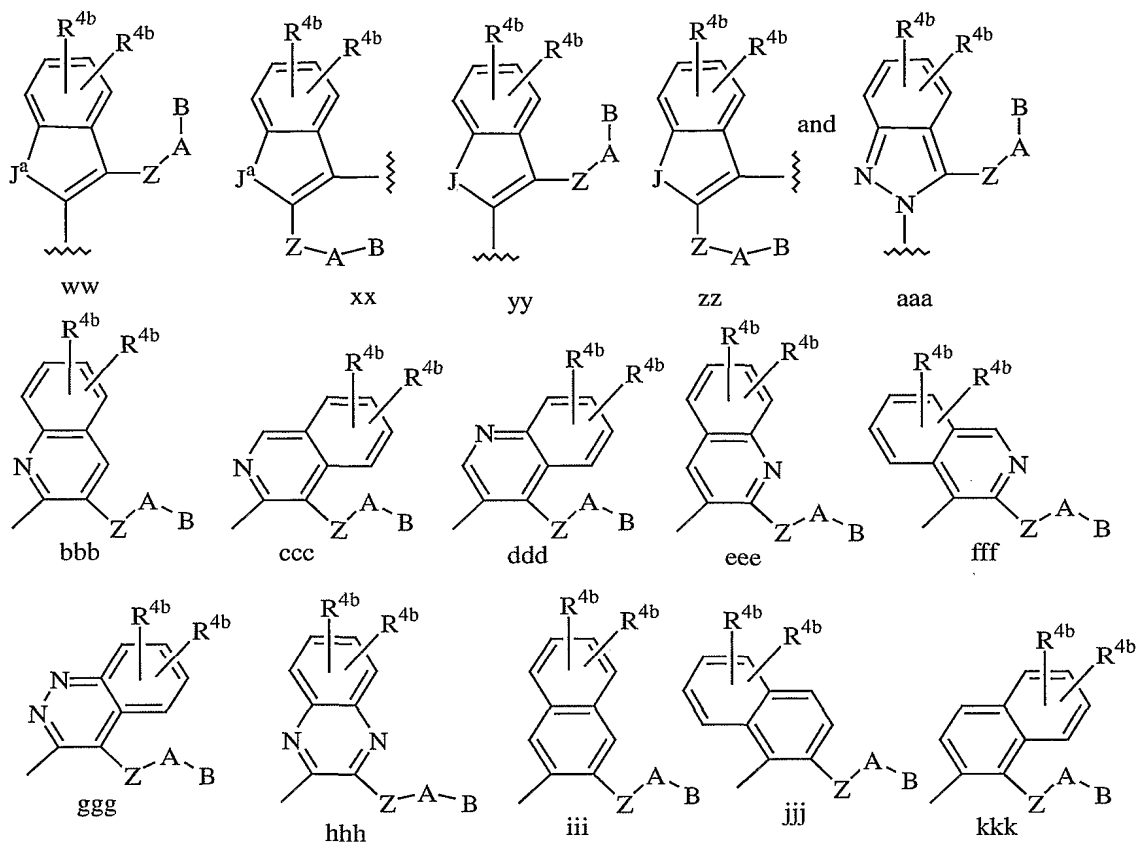
In another embodiment, the present invention provides a novel compound wherein M is selected from the group:

15







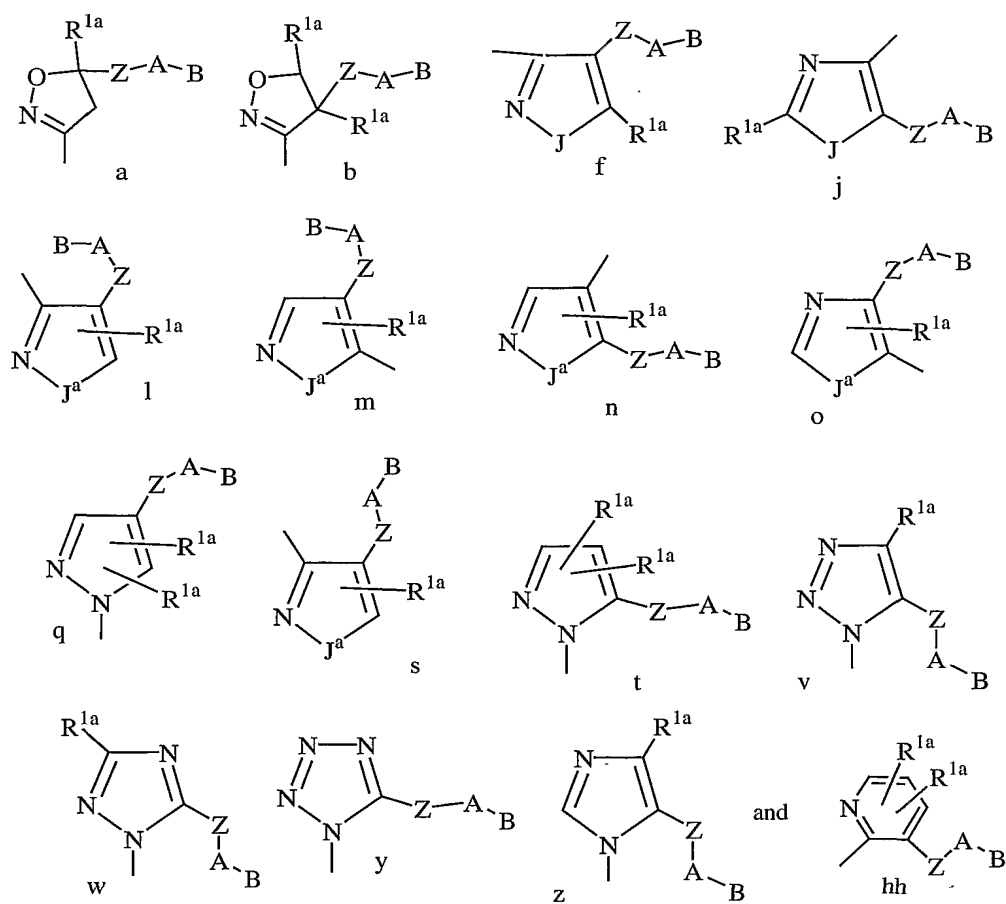


J is O or S; and,

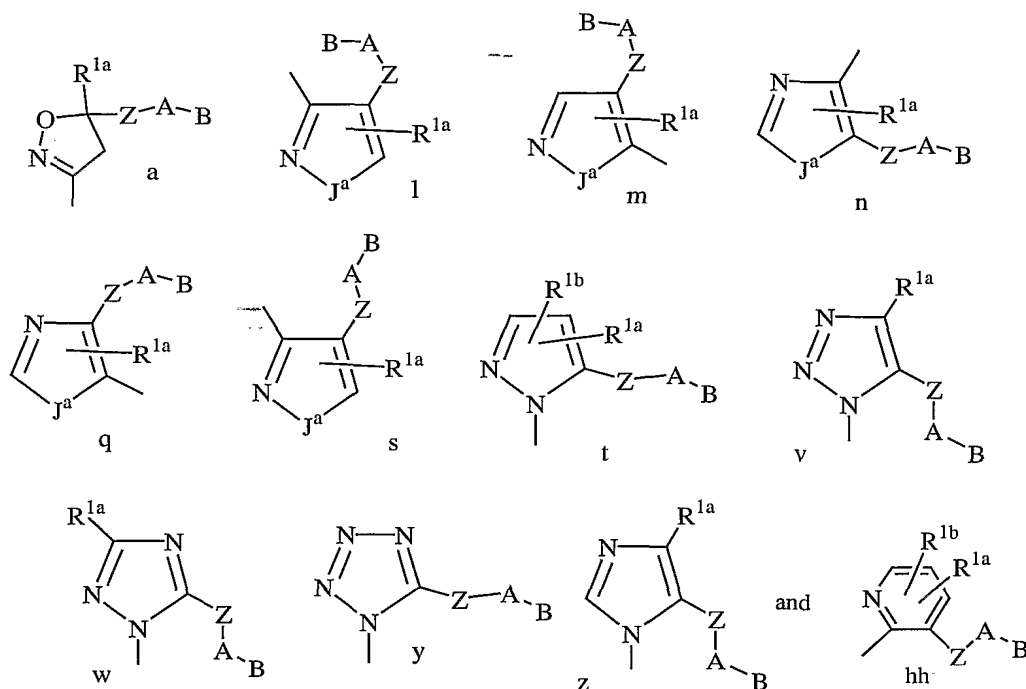
5 J^a is NH or NR^{1a} .

In another embodiment, the present invention provides a novel compound wherein M is selected from the group:

10



In another embodiment, the present invention provides a
 5 novel compound wherein M is selected from the group:



In another embodiment, the present invention provides a novel compound wherein A is selected from one of the following carbocyclic and heterocyclic systems that are substituted with 0-2 R^4 ;

phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, benzofuranyl, benzothiofuranyl, indolyl, benzimidazolyl, benzoxazolyl, benzthiazolyl, indazolyl, benzisoxazolyl, benzisothiazolyl, and isoindazolyl;

In another embodiment, the present invention provides a novel compound wherein A is selected from phenyl, piperidinyl, pyridyl, and pyrimidyl, and is substituted with 0-2 R⁴.

5

In another embodiment, the present invention provides a novel compound wherein A is selected from the group: phenyl, piperidinyl, 2-pyridyl, 3-pyridyl, 2-pyrimidyl, 2-Cl-phenyl, 10 3-Cl-phenyl, 2-F-phenyl, 3-F-phenyl, 2-methylphenyl, 2-aminophenyl, and 2-methoxyphenyl.

In another embodiment, the present invention provides a 15 novel compound wherein:

B is selected from: H, Y, and X-Y, provided that Z and B are attached to different atoms on A;

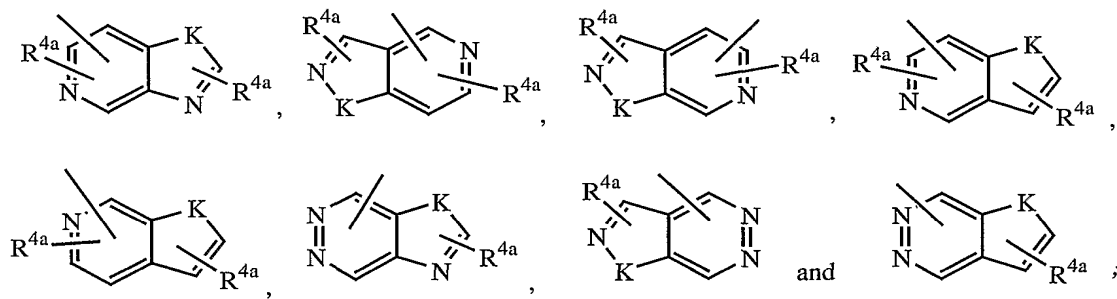
20 X is selected from $-(CR^2R^{2a})_{1-4}-$, $-C(O)-$, $-C(=NR^{1c})-$, $-CR^2(NR^{1c}R^2)-$, $-C(O)CR^2R^{2a}-$, $-CR^2R^{2a}C(O)-$, $-C(O)NR^2-$, $-NR^2C(O)-$, $-C(O)NR^2CR^2R^{2a}-$, $-NR^2C(O)CR^2R^{2a}-$, $-CR^2R^{2a}C(O)NR^2-$, $-CR^2R^{2a}NR^2C(O)-$, $-NR^2C(O)NR^2-$, $-NR^2-$, $-NR^2CR^2R^{2a}-$, $-CR^2R^{2a}NR^2-$, O, $-CR^2R^{2a}O-$, and $-OCR^2R^{2a}-$;

25

Y is selected from one of the following carbocyclic and heterocyclic systems that are substituted with 0-2 R^{4a}; cyclopropyl, cyclopentyl, cyclohexyl, phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, 30 morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, isoxazolinyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 35 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl,

1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl,
 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl,
 1,2,5-triazolyl, 1,3,4-triazolyl, benzofuranyl,
 benzothiofuranyl, indolyl, benzimidazolyl,
 5 benzoxazolyl, benzthiazolyl, indazolyl, benzisoxazolyl,
 benzisothiazolyl, and isoindazolyl;

alternatively, Y is selected from the following bicyclic
 heteroaryl ring systems:



K is selected from O, S, NH, and N.

15 In another embodiment, the present invention provides a
 novel compound wherein:

Y is selected from one of the following carbocyclic and
 heterocyclic systems which are substituted with 0-2 R^{4a};

20 phenyl, piperidiny, piperaziny, pyridyl,
 pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl,
 pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl,
 isothiazolyl, pyrazolyl, imidazolyl, oxadiazole,
 thiadiazole, triazole, 1,2,3-oxadiazole, 1,2,4-
 25 oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 1,2,3-
 thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole,
 1,3,4-thiadiazole, 1,2,3-triazole, 1,2,4-triazole,
 1,2,5-triazole, 1,3,4-triazole, benzofuran,
 benzothiofuran, indole, benzimidazole, benzimidazolone,

benzoxazole, benzthiazole, indazole, benzisoxazole, benzisothiazole, and isoindazole.

5 In another embodiment, the present invention provides a novel compound wherein B is selected from phenyl, pyrrolidino, N-pyrrolidino-carbonyl, morpholino, N-morpholino-carbonyl, 1,2,3-triazolyl, imidazolyl, and benzimidazolyl, and is substituted with 0-1 R^{4a}.

10

In another embodiment, the present invention provides a novel compound wherein B is selected from the group: 2-(aminosulfonyl)phenyl, 2-(methyaminosulfonyl)phenyl, 1-pyrrolidinocarbonyl, 2-(methylsulfonyl)phenyl, 2-(N,N-dimethylaminomethyl)phenyl, 2-(N-methylaminomethyl)phenyl, 2-(N-ethyl-N-methylaminomethyl)phenyl, 2-(N-pyrrolidinylmethyl)phenyl, 1-methyl-2-imidazolyl, 2-methyl-1-imidazolyl, 2-(dimethylaminomethyl)-1-imidazolyl, 2-(methylaminomethyl)-1-imidazolyl, 2-(N-(cyclopropylmethyl)aminomethyl)phenyl, 2-(N-(cyclobutyl)aminomethyl)phenyl, 2-(N-(cyclopentyl)aminomethyl)phenyl, 2-(N-(4-hydroxypiperidinyl)methyl)phenyl, and 2-(N-(3-hydroxypyrrolidinyl)methyl)phenyl.

25

In another embodiment, the present invention provides novel pharmaceutical compositions, comprising: a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of the present invention or a pharmaceutically acceptable salt form thereof.

30

In another embodiment, the present invention provides a novel method for treating or preventing a thromboembolic disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutically acceptable salt form thereof.

In another embodiment, the present invention provides a compound of the present invention as described above for use in therapy.

In another embodiment, the present invention provides the use of the present invention as described above for the manufacture of a medicament for the treatment of a thromboembolic disorder.

DEFINITIONS

The compounds herein described may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated. All processes

used to prepare compounds of the present invention and intermediates made therein are considered to be part of the present invention. All tautomers of shown or described compounds are also considered to be part of the present
5 invention.

The term "substituted," as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that
10 the substitution results in a stable compound. When a substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced. Keto substituents are not present on aromatic moieties.

The present invention is intended to include all
15 isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include C-13 and C-14.

20 When any variable (e.g., R^6) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R^6 , then said group may optionally
25 be substituted with up to two R^6 groups and R^6 at each occurrence is selected independently from the definition of R^6 . Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

30 When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then
35 such substituent may be bonded via any atom in such

substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

As used herein, "alkyl" is intended to include both
5 branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. C₁₋₁₀ alkyl, is intended to include C₁, C₂, C₃, C₄, C₅, C₆, C₇, C₈, C₉, and C₁₀ alkyl groups. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl,
10 s-butyl, t-butyl, n-pentyl, and s-pentyl. "Haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen (for example -C_vF_w where v = 1 to 3 and w = 1 to (2v+1)).
15 Examples of haloalkyl include, but are not limited to, trifluoromethyl, trichloromethyl, pentafluoroethyl, and pentachloroethyl. "Alkoxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. C₁₋₁₀ alkoxy, is intended
20 to include C₁, C₂, C₃, C₄, C₅, C₆, C₇, C₈, C₉, and C₁₀ alkoxy groups. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, n-pentoxy, and s-pentoxy. "Cycloalkyl" is intended to include saturated ring groups, such as cyclopropyl,
25 cyclobutyl, or cyclopentyl. C₃₋₇ cycloalkyl is intended to include C₃, C₄, C₅, C₆, and C₇ cycloalkyl groups. "Alkenyl" is intended to include hydrocarbon chains of either straight or branched configuration and one or more unsaturated carbon-carbon bonds that may occur in any stable point along
30 the chain, such as ethenyl and propenyl. C₂₋₁₀ alkenyl is intended to include C₂, C₃, C₄, C₅, C₆, C₇, C₈, C₉, and C₁₀ alkenyl groups. "Alkynyl" is intended to include hydrocarbon chains of either straight or branched configuration and one or more triple carbon-carbon bonds that may occur in any

stable point along the chain, such as ethynyl and propynyl. C₂₋₁₀ Alkynyl is intended to include C₂, C₃, C₄, C₅, C₆, C₇, C₈, C₉, and C₁₀ alkynyl groups.

"Halo" or "halogen" as used herein refers to fluoro, chloro, bromo, and iodo; and "counterion" is used to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, and sulfate.

As used herein, "carbocycle" or "carbocyclic residue" is intended to mean any stable 3, 4, 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, 10, 11, 12, or 13-membered bicyclic or tricyclic, any of which may be saturated, partially unsaturated, or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, cyclooctyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane, [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, and tetrahydronaphthyl.

As used herein, the term "heterocycle" or "heterocyclic system" is intended to mean a stable 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, or 10-membered bicyclic heterocyclic ring which is saturated, partially unsaturated or unsaturated (aromatic), and which consists of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, NH, O and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized. The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. A nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1,

then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1. As used herein, the term "aromatic heterocyclic system" or "heteroaryl" is intended to mean a stable 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, or 10-membered bicyclic heterocyclic aromatic ring which consists of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, NH, O and S. It is to be noted that total number of S and O atoms in the aromatic heterocycle is not more than 1.

Examples of heterocycles include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzoxazoliny, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazoliny, carbazolyl, 4aH-carbazolyl, carboliny, chromanyl, chromenyl, cinnoliny, decahydroquinoliny, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazoliny, imidazolyl, 1H-indazolyl, indolenyl, indoliny, indoliziny, indoly, 3H-indoly, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindoliny, isoindoly, isoquinoliny, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholiny, naphthyridiny, octahydroisoquinoliny, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxindoly, pyrimidinyl, phenanthridiny, phenanthroliny, phenaziny, phenothiaziny, phenoxathiny, phenoxaziny, phthalaziny, piperaziny, piperidiny, piperidony, 4-piperidony, piperony, pteridiny, puriny, pyranyl, pyraziny, pyrazolidiny, pyrazoliny, pyrazolyl, pyridaziny, pyridooxazole, pyridoimidazole, pyridothiazole, pyridiny, pyridyl, pyrimidinyl, pyrrolidinyl, pyrroliny, 2H-pyrroly, pyrroly, quinazoliny, quinoliny, 4H-quinoliziny,

quinoxaliny1, quinuclidiny1, tetrahydrofurany1,
tetrahydroisoquinoliny1, tetrahydroquinoliny1, tetrazoly1,
6H-1,2,5-thiadiaziny1, 1,2,3-thiadiazoly1, 1,2,4-
thiadiazoly1, 1,2,5-thiadiazoly1, 1,3,4-thiadiazoly1,
5 thianthreny1, thiazoly1, thieny1, thienothiazoly1,
thienooxazoly1, thienoimidazoly1, thiopheny1, triaziny1,
1,2,3-triazoly1, 1,2,4-triazoly1, 1,2,5-triazoly1, 1,3,4-
triazoly1, and xantheny1. Also included are fused ring and
spiro compounds containing, for example, the above
10 heterocycles.

The phrase "pharmaceutically acceptable" is employed
herein to refer to those compounds, materials, compositions,
and/or dosage forms which are, within the scope of sound
medical judgment, suitable for use in contact with the
15 tissues of human beings and animals without excessive
toxicity, irritation, allergic response, or other problem or
complication, commensurate with a reasonable benefit/risk
ratio.

As used herein, "pharmaceutically acceptable salts"
20 refer to derivatives of the disclosed compounds wherein the
parent compound is modified by making acid or base salts
thereof. Examples of pharmaceutically acceptable salts
include, but are not limited to, mineral or organic acid
salts of basic residues such as amines; alkali or organic
25 salts of acidic residues such as carboxylic acids; and the
like. The pharmaceutically acceptable salts include the
conventional non-toxic salts or the quaternary ammonium
salts of the parent compound formed, for example, from non-
toxic inorganic or organic acids. For example, such
30 conventional non-toxic salts include those derived from
inorganic acids such as hydrochloric, hydrobromic, sulfuric,
sulfamic, phosphoric, nitric and the like; and the salts
prepared from organic acids such as acetic, propionic,
succinic, glycolic, stearic, lactic, malic, tartaric,
35 citric, ascorbic, pamoic, maleic, hydroxymaleic,

phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

5 The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in
10 water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby
15 incorporated by reference.

Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (e.g., solubility, bioavailability, manufacturing, etc...) the compounds of the
20 present invention may be delivered in prodrug form. Thus, the present invention is intended to cover prodrugs of the presently claimed compounds, methods of delivering the same and compositions containing the same. "Prodrugs" are intended to include any covalently bonded carriers that
25 release an active parent drug of the present invention *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs the present invention are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine
30 manipulation or *in vivo*, to the parent compound. Prodrugs include compounds of the present invention wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug of the present invention is administered to a mammalian subject, it cleaves to form a
35 free hydroxyl, free amino, or free sulfhydryl group,

respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of the present invention.

5 "Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

10 "Substituted" is intended to indicate that one or more hydrogens on the atom indicated in the expression using "substituted" is replaced with a selection from the indicated group(s), provided that the indicated atom's normal valency is not exceeded, and that the substitution
15 results in a stable compound. When a substituent is keto (i.e., =O) group, then 2 hydrogens on the atom are replaced.

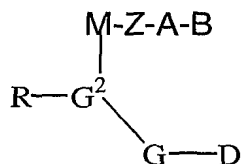
 "Therapeutically effective amount" is intended to include an amount of a compound of the present invention or an amount of the combination of compounds claimed effective
20 to inhibit factor Xa. The combination of compounds is preferably a synergistic combination. Synergy, as described, for example, by Chou and Talalay, *Adv. Enzyme Regul.* **1984**, 22:27-55, occurs when the effect (in this case, inhibition of factor Xa) of the compounds when administered in
25 combination is greater than the additive effect of the compounds when administered alone as a single agent. In general, a synergistic effect is most clearly demonstrated at sub-optimal concentrations of the compounds. Synergy can be in terms of lower cytotoxicity, increased antiviral
30 effect, or some other beneficial effect of the combination compared with the individual components.

SYNTHESIS

 The compounds of the present invention can be prepared
35 in a number of ways known to one skilled in the art of

organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or by variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. The reactions are performed in a solvent appropriate to the reagents and materials employed and suitable for the transformations being effected. It will be understood by those skilled in the art of organic synthesis that the functionality present on the molecule should be consistent with the transformations proposed. This will sometimes require a judgment to modify the order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the invention. It will also be recognized that another major consideration in the planning of any synthetic route in this field is the judicious choice of the protecting group used for protection of the reactive functional groups present in the compounds described in this invention. An authoritative account describing the many alternatives to the trained practitioner is Greene and Wuts (*Protective Groups In Organic Synthesis*, Wiley and Sons, **1991**). All references cited herein are hereby incorporated in their entirety herein by reference.

Scheme 1

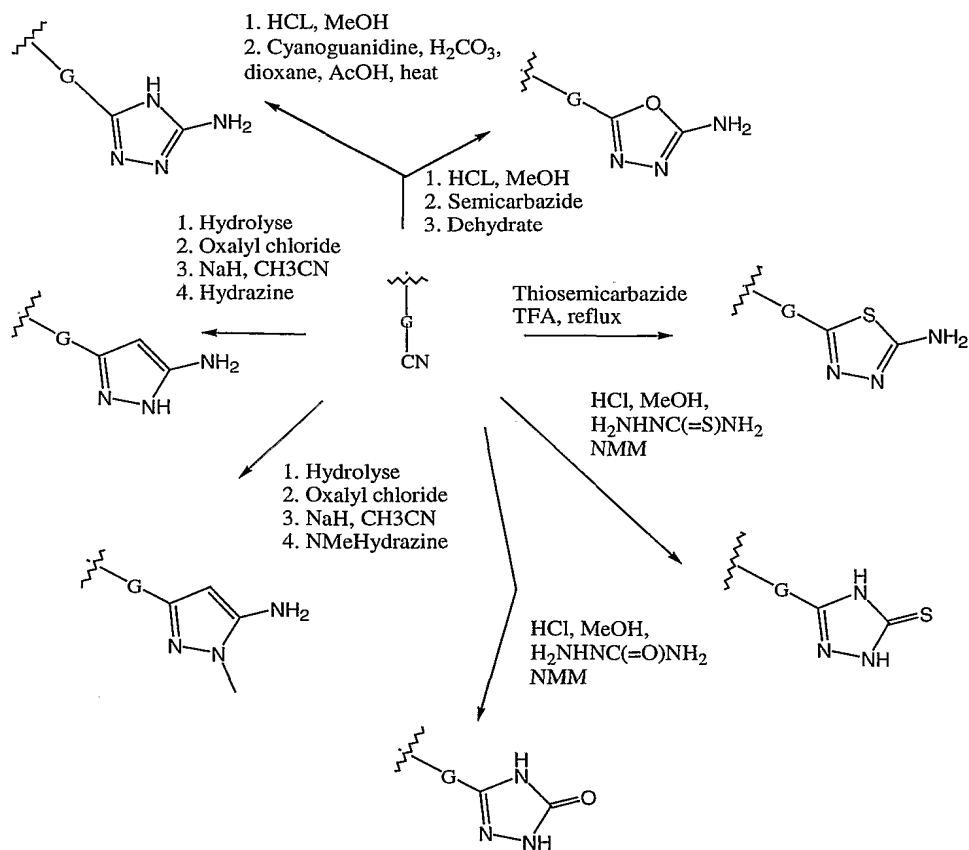


The heterocyclic system shown in Scheme 1 (wherein G-D can be -CN or halo) can be prepared according to the schemes shown in PCT applications WO98/28269, WO98/28282, WO/9857934 and

WO99/32454. In Scheme 1 and the schemes that follow, -G-D represents rings D1, D2, or D3 attached to linker G or precursor to this moiety.

Compounds of this invention wherein G-D is a cyano group can be manipulated to afford thiadiazoles, oxadiazoles, aminooxadiazoles, pyrazoles, triazoles, and triazolones as outlined in Scheme 2.

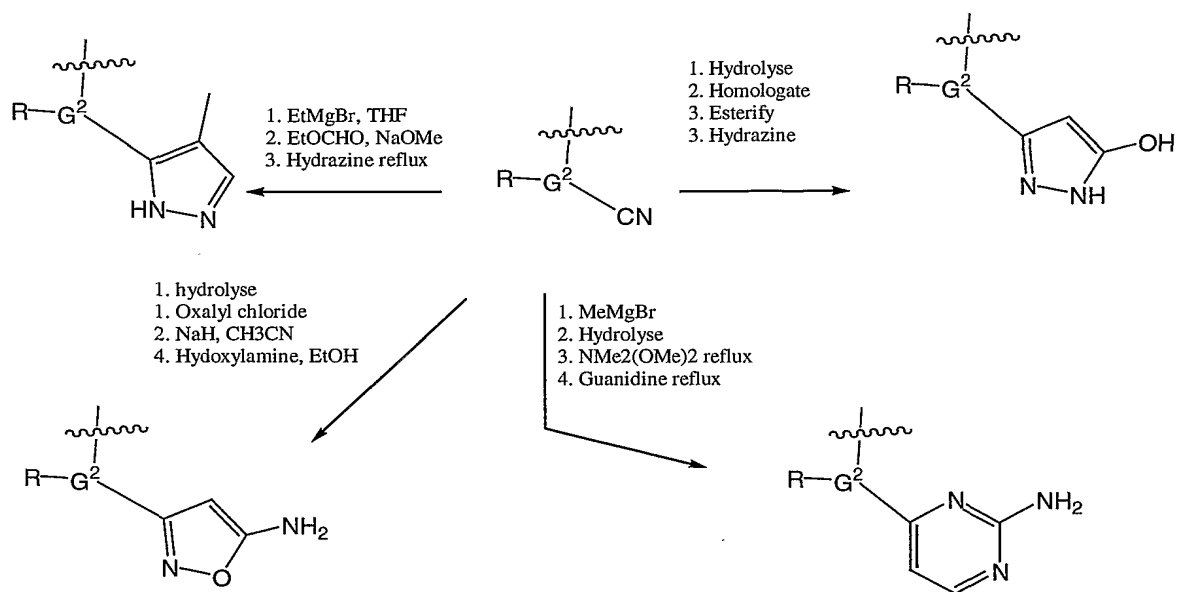
Scheme 2



10

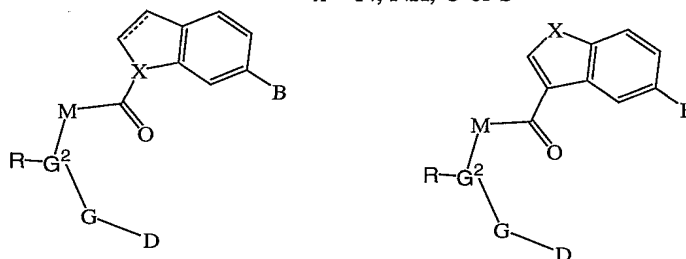
Other heterocycles contained in this invention can also be obtained via methods shown in Scheme 3

Scheme 3



Scheme 4

x = N, NH, O or S



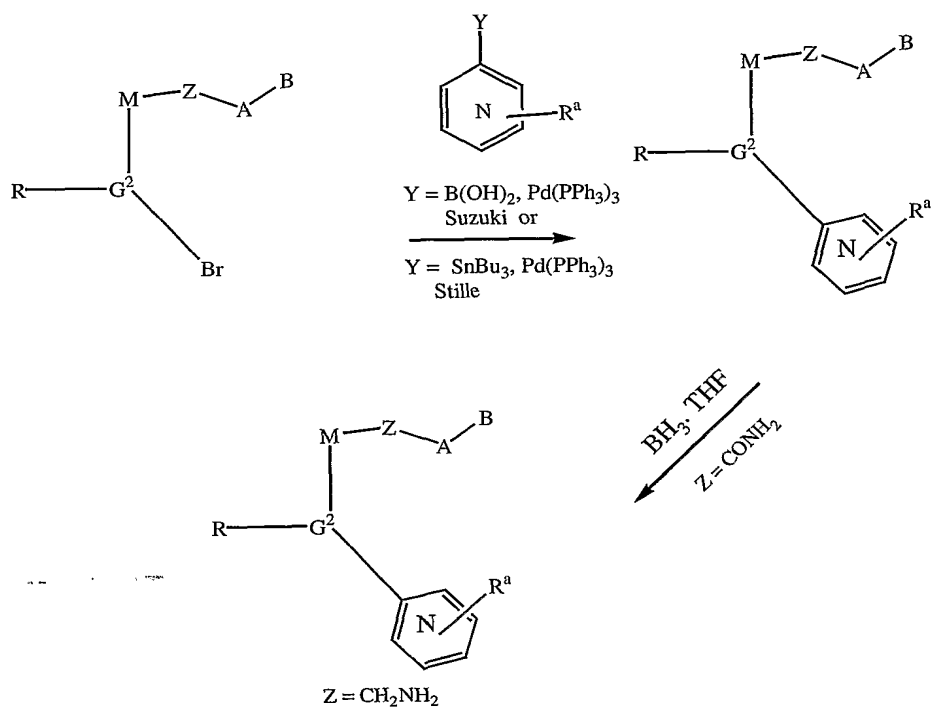
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Various analogs of the compounds contained in Scheme 4 can be made following the methodologies outlined in Schemes 1-3 and WO01/05784.

10 Compounds of this invention wherein ring D is a pyridyl, pyrimidyl, pyridazine, or other heterocyclic ring systems can also be prepared via the Suzuki and or the Stille coupling techniques from easily accessible bromo-phenyl precursors shown in Scheme 5.

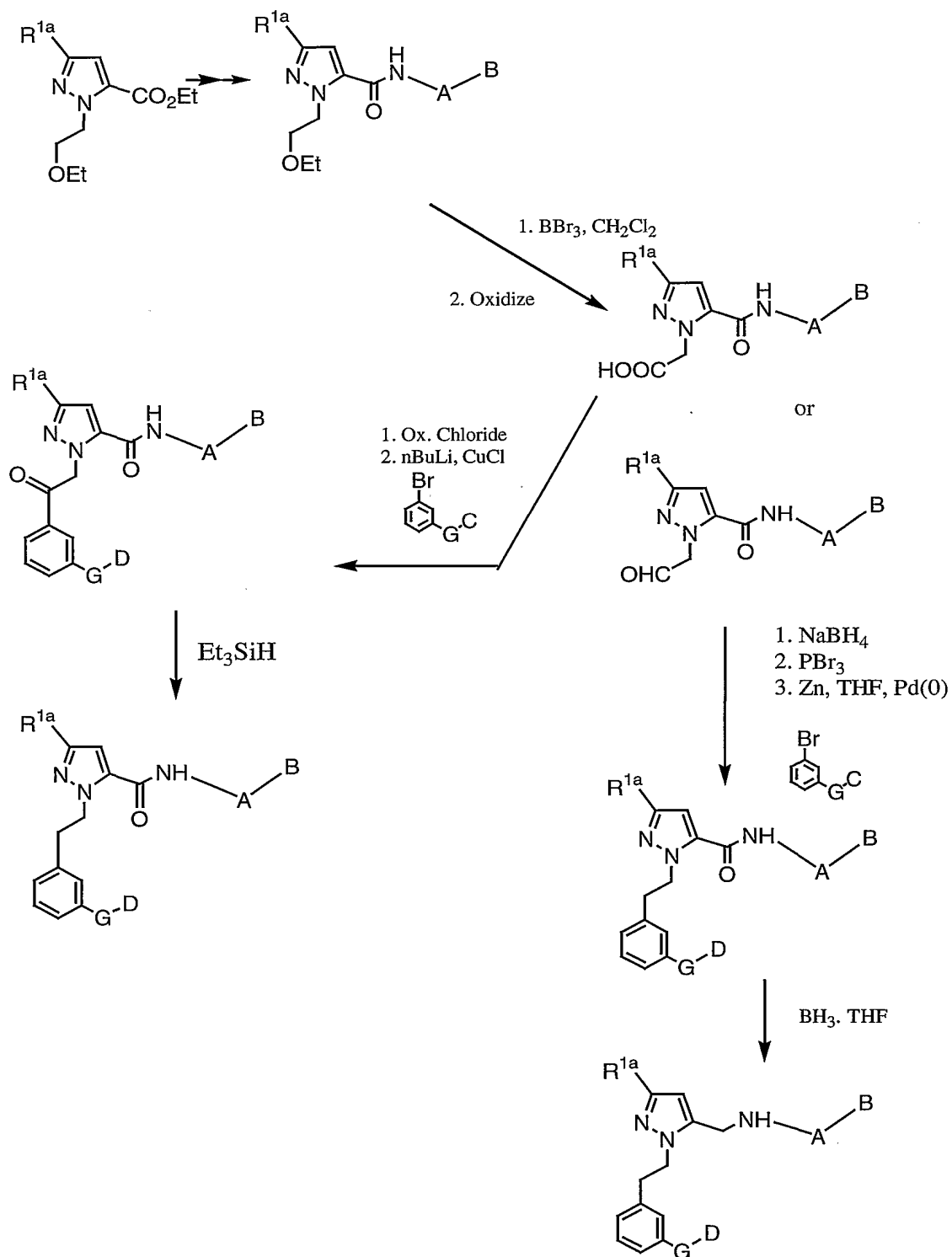
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Scheme 5



Additionally, other compounds of this invention can
 5 also be prepared by those knowledgeable in the art following
 the methodology outlined in Scheme 6.

Scheme 6

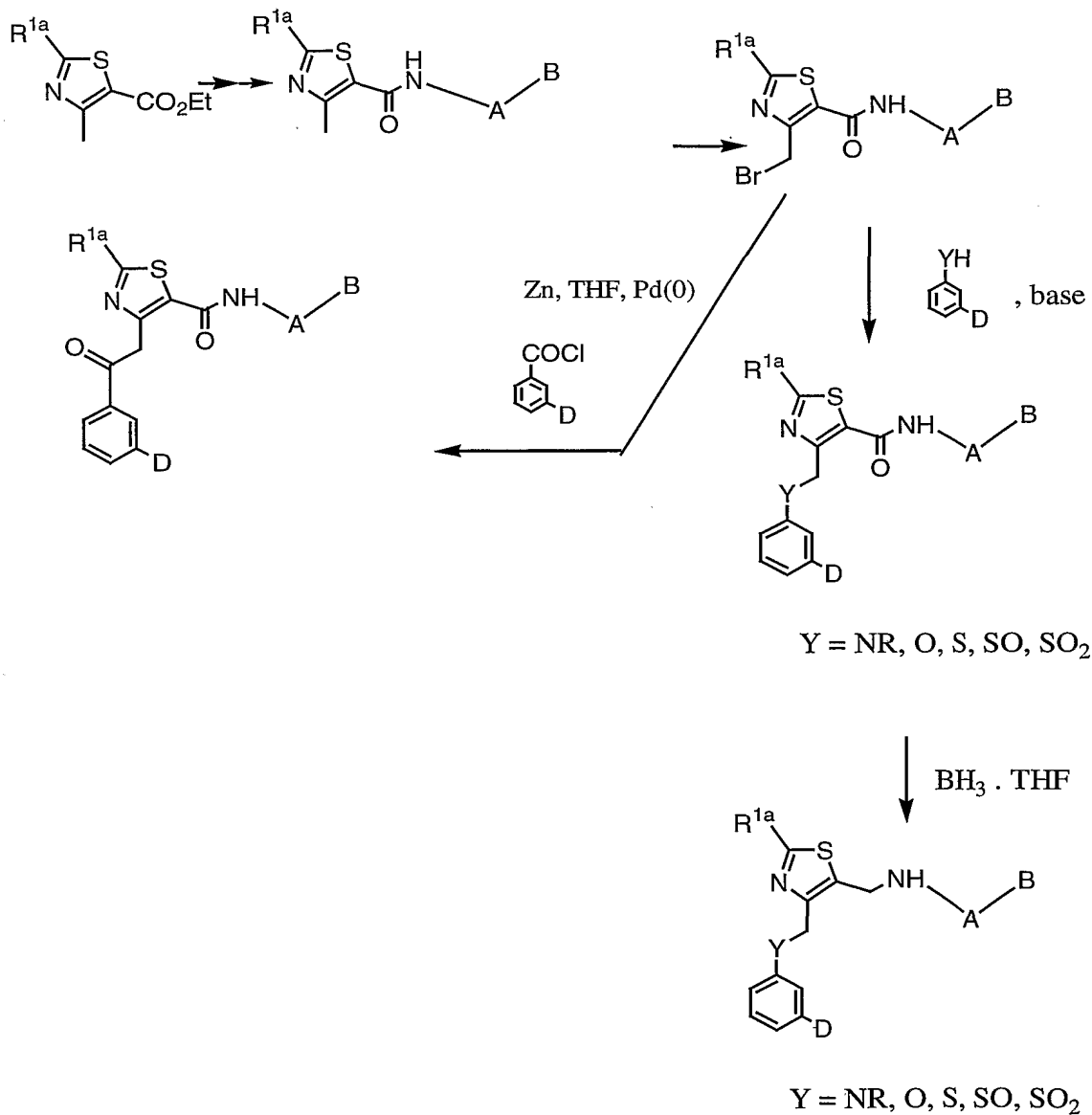


The compounds prepared via Scheme 6 can be used to
 5 prepare similar analogs with other five membered

heterocyclic core systems or other linker G^1 . These can then be further elaborated via the methodologies shown in earlier schemes to obtain compounds of this invention.

For other carbon based heterocyclic or aryl core systems the above methodologies apply but can be further modified via the method outlined in Scheme 7

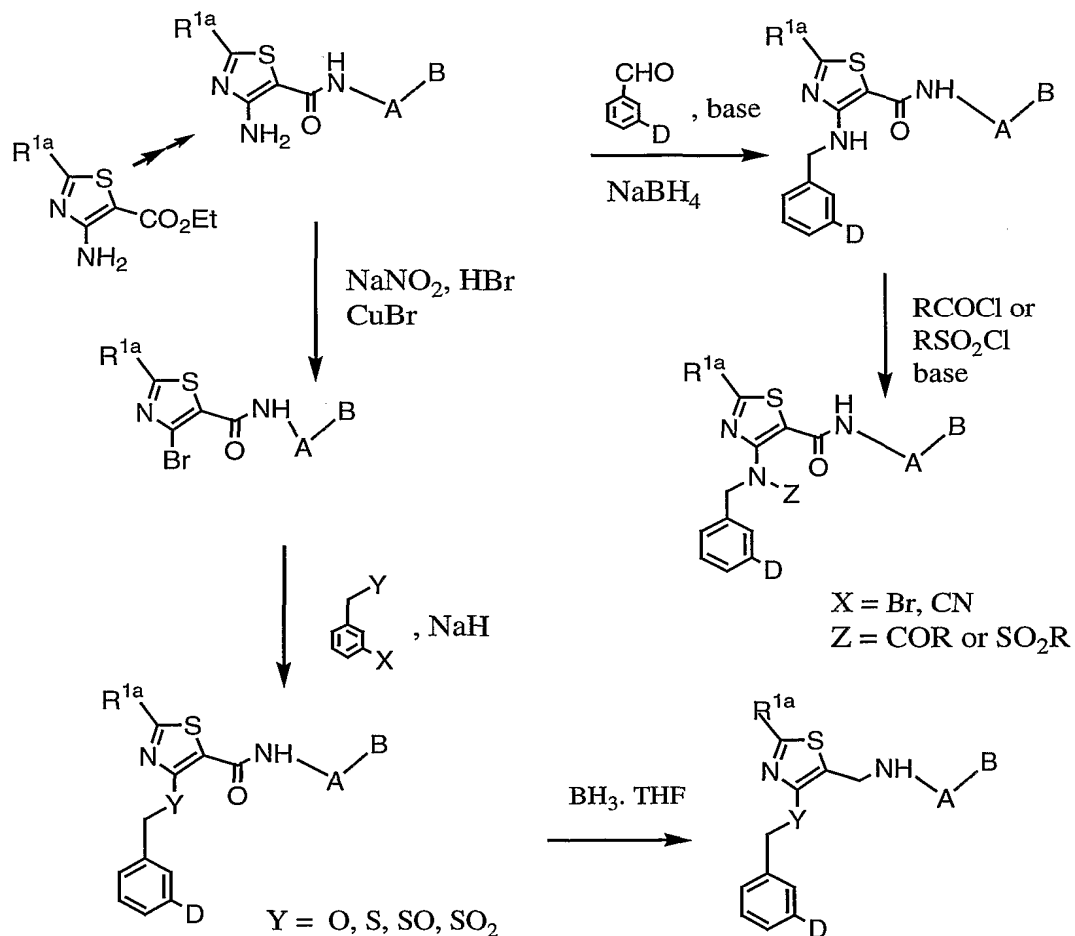
Scheme 7



The synthesis shown in Scheme 7 can be adopted for other carbon based heterocycles or aryl rings. In addition to the above other compounds of this invention can also be prepared via the method outlined in Scheme 8.

5

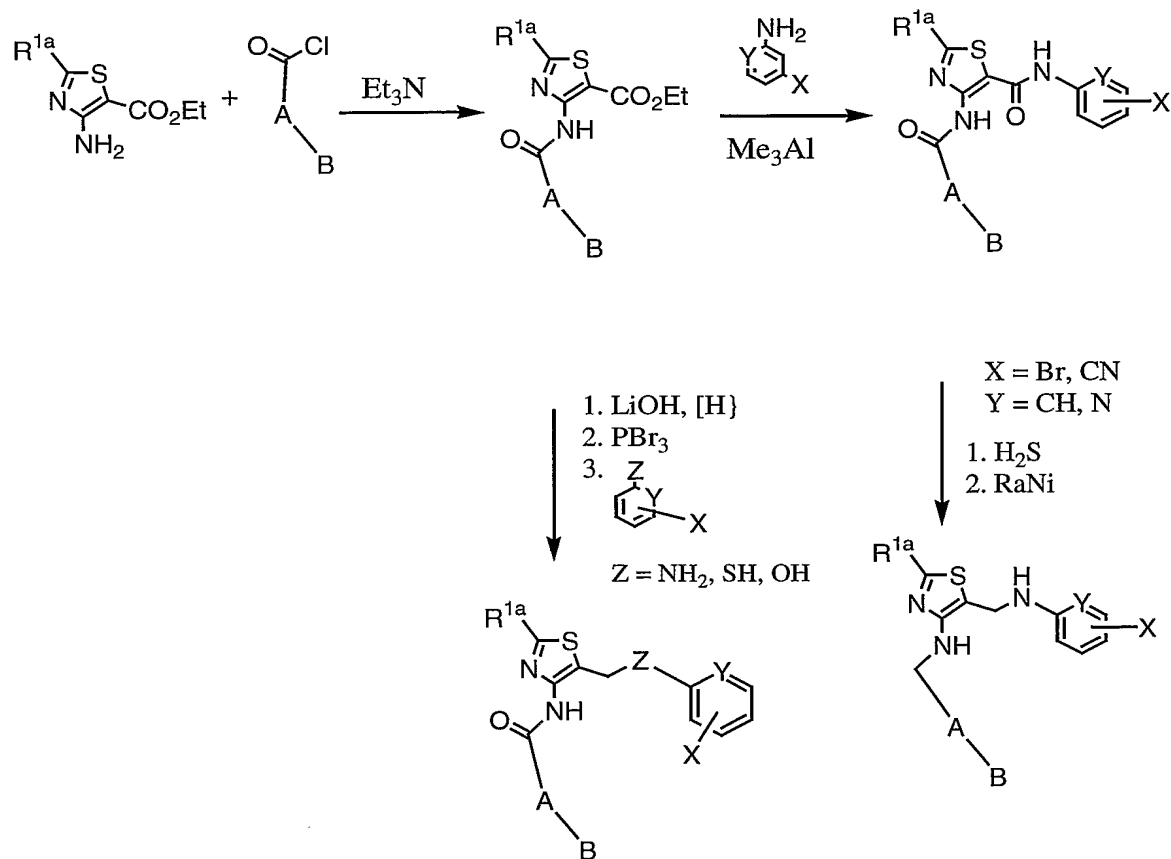
Scheme 8



10

Alternatively, compounds of these inventions can also be prepared via the methodology outlined in Scheme 9.

Scheme 9



5 The synthetic methodology applied in Scheme 9 can also
 be applied to all other heterocyclic or aryl systems. In
 all the cases and schemes provided the intermediates wherein
 X (or D-G-) is a halogen or cyano group these in turn can be
 manipulated to the heterocyclic systems contained in this
 10 invention.

15 The compounds of the present invention have a group "A-B"
 attached to ring M directly or via Z. Preparations of some of
 the rings M and the "A-B" moieties can follow the same methods
 described in WO97/23212, WO97/30971, WO97/38984, WO98/01428,
 WO98/06694, WO98/28269, WO98/28282, WO98/57934, WO98/57937, and
 WO98/57951, the contents of which are incorporated herein by
 reference

UTILITY

The compounds of this invention are useful as anticoagulants for the treatment or prevention of thromboembolic disorders in mammals. The term "thromboembolic disorders" as used herein includes arterial or venous cardiovascular or cerebrovascular thromboembolic disorders, including, for example, unstable angina, first or recurrent myocardial infarction, ischemic sudden death, transient ischemic attack, stroke, atherosclerosis, venous thrombosis, deep vein thrombosis, thrombophlebitis, arterial embolism, coronary and cerebral arterial thrombosis, cerebral embolism, kidney embolisms, and pulmonary embolisms. The anticoagulant effect of compounds of the present invention is believed to be due to inhibition of factor Xa or thrombin.

The effectiveness of compounds of the present invention as inhibitors of factor Xa was determined using purified human factor Xa and synthetic substrate. The rate of factor Xa hydrolysis of chromogenic substrate S2222 (Kabi Pharmacia, Franklin, OH) was measured both in the absence and presence of compounds of the present invention. Hydrolysis of the substrate resulted in the release of pNA, which was monitored spectrophotometrically by measuring the increase in absorbance at 405 nM. A decrease in the rate of absorbance change at 405 nm in the presence of inhibitor is indicative of enzyme inhibition. The results of this assay are expressed as inhibitory constant, K_i .

Factor Xa determinations were made in 0.10 M sodium phosphate buffer, pH 7.5, containing 0.20 M NaCl, and 0.5% PEG 8000. The Michaelis constant, K_m , for substrate hydrolysis was determined at 25°C using the method of Lineweaver and Burk. Values of K_i were determined by allowing 0.2-0.5 nM human factor Xa (Enzyme Research Laboratories, South Bend, IN) to react with the substrate

(0.20 mM-1 mM) in the presence of inhibitor. Reactions were allowed to go for 30 minutes and the velocities (rate of absorbance change vs time) were measured in the time frame of 25-30 minutes. The following relationship was used to calculate K_i values:

$$(v_0 - v_s) / v_s = I / (K_i (1 + S / K_m))$$

where:

v_0 is the velocity of the control in the absence of inhibitor;

10 v_s is the velocity in the presence of inhibitor;

I is the concentration of inhibitor;

K_i is the dissociation constant of the enzyme:inhibitor complex;

S is the concentration of substrate;

15 K_m is the Michaelis constant.

Using the methodology described above, some compounds of the present invention were found to exhibit a K_i of $\leq 10 \mu\text{M}$, thereby confirming the utility of the compounds of the present invention as effective Xa inhibitors.

20 Compounds tested in the above assay are considered to be active if they exhibit a K_i of $\leq 10 \mu\text{M}$. Preferred compounds of the present invention have K_i 's of $\leq 1 \mu\text{M}$. More preferred compounds of the present invention have K_i 's of $\leq 0.1 \mu\text{M}$. Even more preferred compounds of the present invention have K_i 's of $\leq 0.01 \mu\text{M}$. Still more preferred compounds of the present invention have K_i 's of $\leq 0.001 \mu\text{M}$.

The antithrombotic effect of compounds of the present invention can be demonstrated in a rabbit arterio-venous (AV) shunt thrombosis model. In this model, rabbits weighing 30 2-3 kg anesthetized with a mixture of xylazine (10 mg/kg i.m.) and ketamine (50 mg/kg i.m.) are used. A saline-filled AV shunt device is connected between the femoral arterial and the femoral venous cannulae. The AV shunt device consists of a piece of 6-cm tygon tubing that contains a

piece of silk thread. Blood will flow from the femoral artery via the AV-shunt into the femoral vein. The exposure of flowing blood to a silk thread will induce the formation of a significant thrombus. After forty minutes, the shunt is
5 disconnected and the silk thread covered with thrombus is weighed. Test agents or vehicle will be given (i.v., i.p., s.c., or orally) prior to the opening of the AV shunt. The percentage inhibition of thrombus formation is determined for each treatment group. The ID50 values (dose which
10 produces 50% inhibition of thrombus formation) are estimated by linear regression.

The compounds of the present invention may also be useful as inhibitors of serine proteases, notably human thrombin, plasma kallikrein and plasmin. Because of their
15 inhibitory action, these compounds are indicated for use in the prevention or treatment of physiological reactions, blood coagulation and inflammation, catalyzed by the aforesaid class of enzymes. Specifically, the compounds have utility as drugs for the treatment of diseases arising from
20 elevated thrombin activity such as myocardial infarction, and as reagents used as anticoagulants in the processing of blood to plasma for diagnostic and other commercial purposes.

Some compounds of the present invention were shown to
25 be direct acting inhibitors of the serine protease thrombin by their ability to inhibit the cleavage of small molecule substrates by thrombin in a purified system. *In vitro* inhibition constants were determined by the method described by Kettner et al. in *J. Biol. Chem.* **1990**, 265, 18289-18297,
30 herein incorporated by reference. In these assays, thrombin-mediated hydrolysis of the chromogenic substrate S2238 (Helena Laboratories, Beaumont, TX) was monitored spectrophotometrically. Addition of an inhibitor to the assay mixture results in decreased absorbance and is
35 indicative of thrombin inhibition. Human thrombin (Enzyme

Research Laboratories, Inc., South Bend, IN) at a concentration of 0.2 nM in 0.10 M sodium phosphate buffer, pH 7.5, 0.20 M NaCl, and 0.5% PEG 6000, was incubated with various substrate concentrations ranging from 0.20 to 0.02 mM. After 25 to 30 minutes of incubation, thrombin activity was assayed by monitoring the rate of increase in absorbance at 405 nm that arises owing to substrate hydrolysis. Inhibition constants were derived from reciprocal plots of the reaction velocity as a function of substrate concentration using the standard method of Lineweaver and Burk. Using the methodology described above, some compounds of this invention were evaluated and found to exhibit a K_i of less than 10 μ M, thereby confirming the utility of the compounds of the present invention as effective thrombin inhibitors.

The compounds of the present invention can be administered alone or in combination with one or more additional therapeutic agents. These include other anti-coagulant or coagulation inhibitory agents, anti-platelet or platelet inhibitory agents, thrombin inhibitors, or thrombolytic or fibrinolytic agents.

The compounds are administered to a mammal in a therapeutically effective amount. By "therapeutically effective amount" it is meant an amount of a compound of the present invention that, when administered alone or in combination with an additional therapeutic agent to a mammal, is effective to prevent or ameliorate the thromboembolic disease condition or the progression of the disease.

By "administered in combination" or "combination therapy" it is meant that the compound of the present invention and one or more additional therapeutic agents are administered concurrently to the mammal being treated. When administered in combination each component may be administered at the same time or sequentially in any order

at different points in time. Thus, each component may be administered separately but sufficiently closely in time so as to provide the desired therapeutic effect. Other anticoagulant agents (or coagulation inhibitory agents) that may be used in combination with the compounds of this invention include warfarin and heparin, as well as other factor Xa inhibitors such as those described in the publications identified above under Background of the Invention.

The term anti-platelet agents (or platelet inhibitory agents), as used herein, denotes agents that inhibit platelet function such as by inhibiting the aggregation, adhesion or granular secretion of platelets. Such agents include, but are not limited to, the various known non-steroidal anti-inflammatory drugs (NSAIDS) such as aspirin, ibuprofen, naproxen, sulindac, indomethacin, mefenamate, droxicam, diclofenac, sulfinpyrazone, and piroxicam, including pharmaceutically acceptable salts or prodrugs thereof. Of the NSAIDS, aspirin (acetylsalicyclic acid or ASA), and piroxicam are preferred. Other suitable anti-platelet agents include ticlopidine, including pharmaceutically acceptable salts or prodrugs thereof. Ticlopidine is also a preferred compound since it is known to be gentle on the gastro-intestinal tract in use. Still other suitable platelet inhibitory agents include IIb/IIIa antagonists, thromboxane-A₂-receptor antagonists and thromboxane-A₂-synthetase inhibitors, as well as pharmaceutically acceptable salts or prodrugs thereof.

The term thrombin inhibitors (or anti-thrombin agents), as used herein, denotes inhibitors of the serine protease thrombin. By inhibiting thrombin, various thrombin-mediated processes, such as thrombin-mediated platelet activation (that is, for example, the aggregation of platelets, and/or the granular secretion of plasminogen activator inhibitor-1 and/or serotonin) and/or fibrin formation are disrupted. A

number of thrombin inhibitors are known to one of skill in the art and these inhibitors are contemplated to be used in combination with the present compounds. Such inhibitors include, but are not limited to, boroarginine derivatives, boro peptides, heparins, hirudin and argatroban, including pharmaceutically acceptable salts and prodrugs thereof.

Boroarginine derivatives and boro peptides include N-acetyl and peptide derivatives of boronic acid, such as C-terminal α -aminoboronic acid derivatives of lysine, ornithine,

arginine, homoarginine and corresponding isothiuronium analogs thereof. The term hirudin, as used herein, includes suitable derivatives or analogs of hirudin, referred to herein as hirulogs, such as disulfatohirudin. Boro peptide thrombin inhibitors include compounds described in Kettner et al., U.S. Patent No. 5,187,157 and European Patent Application Publication Number 293 881 A2, the disclosures of which are hereby incorporated herein by reference. Other suitable boroarginine derivatives and boro peptide thrombin inhibitors include those disclosed in PCT Application Publication Number 92/07869 and European Patent Application Publication Number 471,651 A2, the disclosures of which are hereby incorporated herein by reference.

The term thrombolytics (or fibrinolytic) agents (or thrombolytics or fibrinolytics), as used herein, denotes agents that lyse blood clots (thrombi). Such agents include tissue plasminogen activator, anistreplase, urokinase or streptokinase, including pharmaceutically acceptable salts or prodrugs thereof. The term anistreplase, as used herein, refers to anisoylated plasminogen streptokinase activator complex, as described, for example, in European Patent Application No. 028,489, the disclosure of which is hereby incorporated herein by reference herein. The term urokinase, as used herein, is intended to denote both dual and single chain urokinase, the latter also being referred to herein as prourokinase.

Administration of the compounds of the present invention in combination with such additional therapeutic agent, may afford an efficacy advantage over the compounds and agents alone, and may do so while permitting the use of lower doses of each. A lower dosage minimizes the potential of side effects, thereby providing an increased margin of safety.

The compounds of the present invention are also useful as standard or reference compounds, for example as a quality standard or control, in tests or assays involving the inhibition of factor Xa. Such compounds may be provided in a commercial kit, for example, for use in pharmaceutical research involving factor Xa. For example, a compound of the present invention could be used as a reference in an assay to compare its known activity to a compound with an unknown activity. This would ensure the experimenter that the assay was being performed properly and provide a basis for comparison, especially if the test compound was a derivative of the reference compound. When developing new assays or protocols, compounds according to the present invention could be used to test their effectiveness.

The compounds of the present invention may also be used in diagnostic assays involving factor Xa. For example, the presence of factor Xa in an unknown sample could be determined by addition of chromogenic substrate S2222 to a series of solutions containing test sample and optionally one of the compounds of the present invention. If production of pNA is observed in the solutions containing test sample, but not in the presence of a compound of the present invention, then one would conclude factor Xa was present.

Dosage and Formulation

The compounds of this invention can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release or timed release

formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. They may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts. They can be administered alone, but generally will be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage regimen for the compounds of the present invention will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; the route of administration, the renal and hepatic function of the patient, and the effect desired. A physician or veterinarian can determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the thromboembolic disorder.

By way of general guidance, the daily oral dosage of each active ingredient, when used for the indicated effects, will range between about 0.001 to 1000 mg/kg of body weight, preferably between about 0.01 to 100 mg/kg of body weight per day, and most preferably between about 1.0 to 20 mg/kg/day. Intravenously, the most preferred doses will range from about 1 to about 10 mg/kg/minute during a constant rate infusion. Compounds of this invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily.

Compounds of this invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using transdermal skin

patches. When administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

5 The compounds are typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers (collectively referred to herein as pharmaceutical carriers) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules,
10 elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert
15 carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically
20 acceptable inert carrier such as ethanol, glycerol, water, and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as
25 glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate,
30 sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

35 The compounds of the present invention can also be administered in the form of liposome delivery systems, such

as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

5 Compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxide-
10 polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic
15 acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihdropyrans, polycyanoacrylates, and crosslinked or amphipathic block copolymers of hydrogels.

Dosage forms (pharmaceutical compositions) suitable for
20 administration may contain from about 1 milligram to about 100 milligrams of active ingredient per dosage unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition.

25 Gelatin capsules may contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained
30 release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols
5 such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents
10 such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben,
15 and chlorobutanol.

Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in this field.

Representative useful pharmaceutical dosage-forms for
20 administration of the compounds of this invention can be illustrated as follows:

Capsules

A large number of unit capsules can be prepared by filling standard two-piece hard gelatin capsules each with
25 100 milligrams of powdered active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

Soft Gelatin Capsules

A mixture of active ingredient in a digestable oil
30 such as soybean oil, cottonseed oil or olive oil may be prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules should be washed and dried.

Tablets

Tablets may be prepared by conventional procedures so that the dosage unit is 100 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

Injectable

A parenteral composition suitable for administration by injection may be prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol and water. The solution should be made isotonic with sodium chloride and sterilized.

Suspension

An aqueous suspension can be prepared for oral administration so that each 5 mL contain 100 mg of finely divided active ingredient, 200 mg of sodium carboxymethyl cellulose, 5 mg of sodium benzoate, 1.0 g of sorbitol solution, U.S.P., and 0.025 mL of vanillin.

Where the compounds of this invention are combined with other anticoagulant agents, for example, a daily dosage may be about 0.1 to 100 milligrams of the compound of the present invention and about 1 to 7.5 milligrams of the second anticoagulant, per kilogram of patient body weight. For a tablet dosage form, the compounds of this invention generally may be present in an amount of about 5 to 10 milligrams per dosage unit, and the second anti-coagulant in an amount of about 1 to 5 milligrams per dosage unit.

Where the compounds of the present invention are administered in combination with an anti-platelet agent, by way of general guidance, typically a daily dosage may be about 0.01 to 25 milligrams of the compound of the present invention and about 50 to 150 milligrams of the anti-platelet agent, preferably about 0.1 to 1 milligrams of the

compound of the present invention and about 1 to 3 milligrams of anti-platelet agents, per kilogram of patient body weight.

Where the compounds of the present invention are administered in combination with thrombolytic agent, typically a daily dosage may be about 0.1 to 1 milligrams of the compound of the present invention, per kilogram of patient body weight and, in the case of the thrombolytic agents, the usual dosage of the thrombolytic agent when administered alone may be reduced by about 70-80% when administered with a compound of the present invention.

Where two or more of the foregoing second therapeutic agents are administered with the compound of the present invention, generally the amount of each component in a typical daily dosage and typical dosage form may be reduced relative to the usual dosage of the agent when administered alone, in view of the additive or synergistic effect of the therapeutic agents when administered in combination.

Particularly when provided as a single dosage unit, the potential exists for a chemical interaction between the combined active ingredients. For this reason, when the compound of the present invention and a second therapeutic agent are combined in a single dosage unit they are formulated such that although the active ingredients are combined in a single dosage unit, the physical contact between the active ingredients is minimized (that is, reduced). For example, one active ingredient may be enteric coated. By enteric coating one of the active ingredients, it is possible not only to minimize the contact between the combined active ingredients, but also, it is possible to control the release of one of these components in the gastrointestinal tract such that one of these components is not released in the stomach but rather is released in the intestines. One of the active ingredients may also be coated with a material that effects a sustained-release throughout

the gastrointestinal tract and also serves to minimize physical contact between the combined active ingredients. Furthermore, the sustained-released component can be additionally enteric coated such that the release of this component occurs only in the intestine. Still another approach would involve the formulation of a combination product in which the one component is coated with a sustained and/or enteric release polymer, and the other component is also coated with a polymer such as a low-viscosity grade of hydroxypropyl methylcellulose (HPMC) or other appropriate materials as known in the art, in order to further separate the active components. The polymer coating serves to form an additional barrier to interaction with the other component.

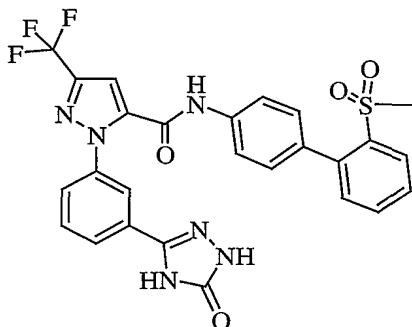
These as well as other ways of minimizing contact between the components of combination products of the present invention, whether administered in a single dosage form or administered in separate forms but at the same time by the same manner, will be readily apparent to those skilled in the art, once armed with the present disclosure.

Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments that are given for illustration of the invention and are not intended to be limiting thereof.

EXAMPLES

Example 1

1-[3-(1',3',4'-Triazol-2'-on-5'-yl)phenyl]-3-trifluoromethyl-5-[(2'-sulfonylmethyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole



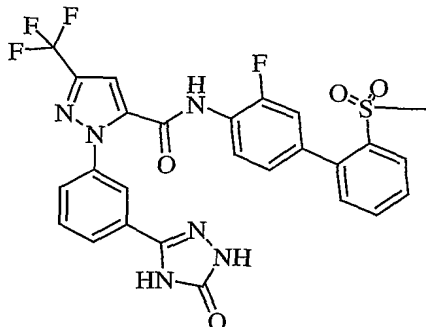
Part A: The starting nitrile, 1-(3-cyanophenyl)-3-trifluoromethyl-5-[(2'-sulfonylmethyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole, was prepared according to the methodology described in W098/28269 (see Example 73). To 0.54 g (1.06 mmol) of this nitrile in anhydrous ethanol was bubbled HCl gas for 0.5h. The reaction mixture was capped and allowed to stir at room temperature for 18h. The ethanol was evaporated to afford the crude ethoxyimide intermediate. LRMS (NH₃-CI) m/z (relative intensity) 557 (M=H, 100).

Part B: To the crude product in dioxane (10 mL) from part A was added N-Methyl morpholine (0.6 mL, 5.03 mmol). To this mixture was added semicarbazide hydrochloride (0.13 g, 1.06 mmol) and the reaction mixture was refluxed gently for 72h. The mixture was cooled, poured in water (100 mL) and the organics were extracted with ethyl acetate (2x50 mL), dried and evaporated to a brown mass. The crude mixture was purified via reverse-phase HPLC to afford the title compound. ¹H NMR (DMSO-d₆, 300MHz) δ: 12.91 (s, 1H), 11.81 (s, 1H), 10.90 (s, 1H), 8.08 (d, 1H, J=7.7Hz), 7.98 (s, 1H), 7.92-7.90 (m, 1H), 7.78-7.64 (m, 7H), 7.41-7.38 (m, 3H),

2.84 (s, 3H) ppm. LRMS (ES⁺): m/z 591 (M+Na). HRMS (ESI): for C₂₆H₂₀SF₃O₄N₆ Mass= 569.1206.

Example 2

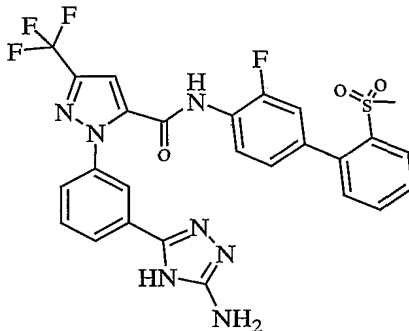
1-[3-(1',3',4'-Triazol-2'-on-5'-yl)phenyl]-3-trifluoromethyl-5-[(3-fluoro-2'-sulfonylmethyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole



The starting nitrile, 1-(3-cyanophenyl)-3-trifluoromethyl-5-[(3-fluoro-2'-sulfonylmethyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole, was prepared according to the methodology described in WO98/28269 (see Example 206). The title compound was prepared from this nitrile in a similar method to that described for Example 1. ¹HNMR (DMSO-d₆, 300MHz) δ: 12.17 (s, 1H), 11.81 (s, 1H), 10.73 (s, 1H), 8.09 (dd, 1H, J₁=J₂=8.0Hz), 7.99 (s, 1H), 7.93-7.90 (m, 1H), 7.81-7.64 (m, 6H), 7.43 (dd, 1H, J₁=J₂=7.0Hz), 7.38 (dd, 1H, J₁=J₂=11.0Hz), 7.24 (d, 1H, J=8.0Hz), 2.92 (s, 3H) ppm. LRMS (ES⁺): m/z 587 (M+H) 609 (M+Na). HRMS (ESI): for C₂₆H₁₉SF₄O₄N₆ Mass= 587.1123.

Example 3

1-[3-(2'-Amino-1',3',4'-triazol-5'-yl)phenyl]-3-trifluoromethyl-5-[(3-fluoro-2'-sulfonylmethyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole trifluoroacetic acid salt



5

Part A: The nitrile employed for Example 2 was utilized for the preparation of Example 3. Hydrogen chloride was bubbled into an ice-cooled solution of the nitrile (0.52 g, 0.98 mmol) in anhydrous ethanol (50 mL) for 0.5h. The reaction mixture was allowed to warm to ambient temperature overnight and then concentrated *in vacuo*. The crude ethyl imidate hydrochloride was placed under high vacuum and used directly in the next step.

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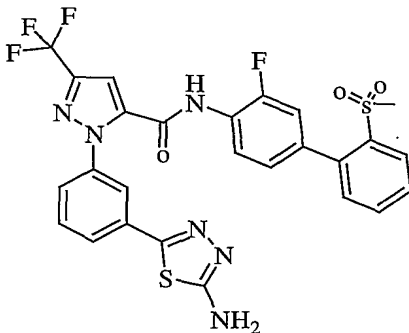
Part B: Acetic acid (1.0 mL) was added to a suspension of crude imidate hydrochloride (0.98 mmol) obtained in part A and aminoguanidine bicarbonate (0.18 g, 1.31 mmol) in 1,4-dioxane (25 mL). The reaction mixture was refluxed for 48h and then concentrated under reduced pressure. The crude solid was purified by reverse phase HPLC. ¹HNMR (DMSO-d₆, 300MHz) δ: 10.74 (s, 1H), 8.88-7.99 (m, 3H), 7.80-7.69 (m, 4H), 7.62-7.60 (m, 2H), 7.44-7.36 (m, 2H), 7.24-7.22 (m, 1H), 2.92 (s, 3H) ppm. LRMS (ES⁺): m/z 586 (M+H) 608 (M+Na). HRMS (ESI): for C₂₆H₂₀SF₄O₃N₆ Mass= 586.1280.

20

25

Example 4

1-[3-(2'-Amino-3',4'-thiadiazol-5'-yl)phenyl]-3-trifluoromethyl-5-[(3-fluoro-2'-sulfonylmethyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole trifluoroacetic acid salt



5

The nitrile employed for Example 2 was dissolved in TFA (2 mL). To this mixture was added thiosemicarbazide (0.13 g, 1.42 mmol) and the reaction mixture was gently refluxed for 2h. The reaction was then concentrated and the crude oil was purified via reverse phase HPLC to afford the title

10

compound. ¹HNMR (DMSO-d₆, 300MHz) δ: 10.73 (s, 1H), 8.10 (d, 1H, J=8.0Hz), 7.95 (s, 1H), 7.87-7.86 (m, 1H), 7.80-7.62 (m, 8H), 7.44 (d, 1H, J=8.0Hz), 7.38 (d, 1H, J=11.0Hz), 7.24 (d, 1H, J=8.0Hz), 2.92 (s, 3H) ppm. LRMS (ES⁺): m/z 625 (M+Na).

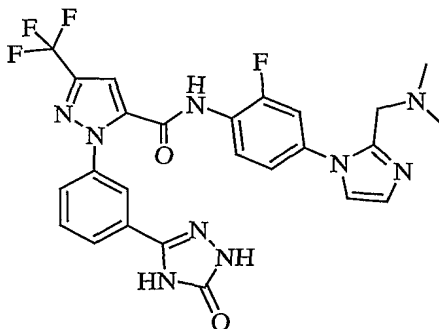
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HRMS (ESI): for C₂₆H₁₉S₂F₄O₃N₆ Mass= 603.0889.

Example 5

1-[3-(1',3',4'-Triazol-2'-on-5'-yl)phenyl]-3-trifluoromethyl-5-[4-(2'-(N,N-dimethylamino)methylimidazol-1'-yl)-2-fluorophenyl]aminocarbonyl]pyrazole trifluoroacetic acid salt

20

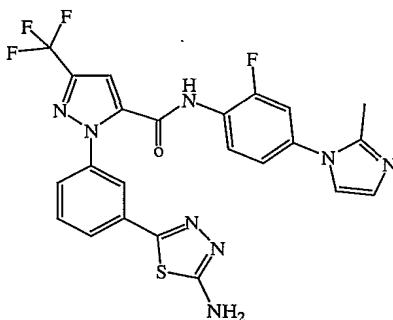


Part A: 1-(3-Cyanophenyl)-3-trifluoromethylpyrazole-5-carboxylic acid was prepared according the methods of WO98/28269 (see Example 14). The pyrazole acid chloride (2.48 mmol) was coupled with 2-fluoro-N,N-dimethyl-2-aminomethyl-4-imidazoloaniline (1.04 g, 2.25 mmol) using DMAP (1.38 g, 11.26 mmol) in dichloromethane. After 48h the reaction mixture was concentrated, dissolved in EtOAc, and washed three times with brine. Then the organics were dried over MgSO₄ and concentrated under reduced pressure. The crude material was purified by flash chromatography. ¹HNMR (DMSO-d₆, 300MHz) δ: 10.72 (s, 1H), 8.16 (s, 1H), 8.01 (d, 1H, J=8Hz), 7.93 (d, 1H, J=8Hz), 7.77-7.69 (m, 4H), 7.51-7.47 (m, 2H), 7.00 (s, 1H), 3.38 (s, 2H), 2.13 (s, 6H) ppm; LRMS: m/z 496 (M-H).

Part B: The coupling product was converted to its corresponding methylimidate via the Pinner reaction. The imidate (1.62 mmol) was then treated with semicarbazide (0.22 g, 1.94 mmol) in refluxing 1,4-dioxane (40 mL) for 48h. The reaction mixture was concentrated to give the crude aminooxadiazole. The product was purified by HPLC. LRMS: m/z 556 (M+H).

Example 6

1-[3-(2'-Amino-3',4'-thiadiazol-5'-yl)phenyl]-3-trifluoromethyl-5-[4-(2'-methylimidazol-1'-yl)-2-fluorophenyl]aminocarbonyl]pyrazole trifluoroacetic acid salt

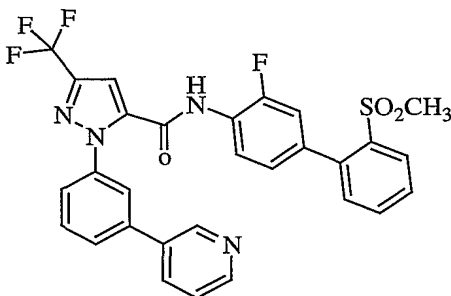


Part A: 1-(3-Cyanophenyl)-3-trifluoromethylpyrazole-5-carboxylic acid was prepared according the methods of WO98/28269 (see Example 14). The pyrazole acid chloride (0.51 mmol) was coupled with 2-methyl-4-imidazoloaniline (1.04 g, 2.25 mmol) using DMAP (0.31 g, 2.49 mmol) in 10 mL dichloromethane. After 24H the reaction mixture was concentrated. The resulting concentrate was dissolved in EtOAc and washed three times with brine. The organics were dried over MgSO₄ and concentrated under reduced pressure. The crude coupling product was used directly. LRMS: m/z 437 (M+H).

Part B: The crude benzonitrile was treated with thiosemicarbazide (0.04 g, 0.45 mmol) in 5 mL refluxing TFA for 4h. The reaction mixture was concentrated and purified by HPLC to give the aminothiadiazole. ¹HNMR (DMSO, 300MHz) δ: 11.07 (s, 1H), 7.95 (s, 1H), 7.89-7.84 (m, 4H), 7.77 (d, 1H, J=2Hz), 7.71 (s, 1H), 7.63-7.55 (m, 4H), 2.50 (s, 3H)ppm; LRMS: m/z 256 (M/2+H), 511 (M+H); HRMS: calc'd for C₂₃H₁₈SO F₃ N₈=511.1288.

Example 7

1-[3-(Pyrid-3'-yl)phenyl]-3-trifluoromethyl-5-[(3-fluoro-2'-sulfonylmethyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole trifluoroacetic acid salt

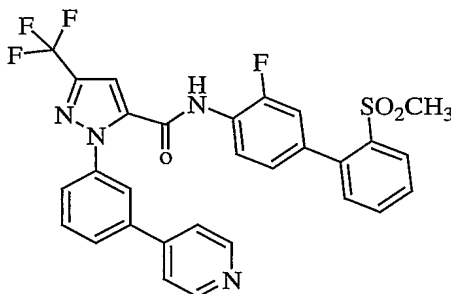


1-(Bromophenyl)-5-(2'-methylsulfonyl-[1,1']-biphen-4-yl)-3-trifluoromethyl-pyrazole was prepared according to the

methods of WO98/28269 (see Example 10, except that 3-methoxy-trichloroacetyl-4,4,4-trifluorocrotonate was used in place of 3-methoxy-trichloroacetylcrotonate). 3-Pyridylboronate (0.112 g, 0.75 mmol) was added to 1-(bromophenyl)-5-(2'-methylsulfonyl-[1,1']-biphen-4-yl)-3-trifluoromethyl-pyrazole (0.366 g, 0.62 mmol) in a solution of Toluene:EtOH (4:1, 50 mL). Sodium carbonate (2M, 0.4 mL) was added and the solution was degassed for 0.5h. To this solution was added Pd(PPh₃)₄ and the solution was gently refluxed for 18h. The solution was concentrated and purified via reverse phase HPLC to afford 0.050g of colorless product. LRMS 581 m/z (rel. intensity), 581 (M+H, 100).

Example 8

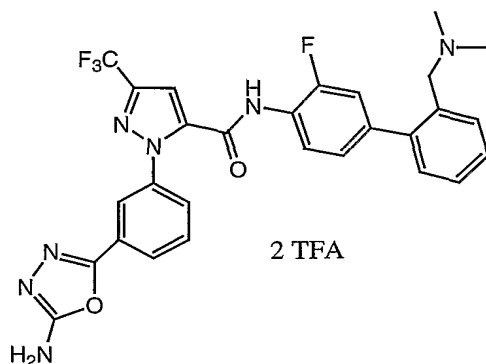
1-[3-(Pyrid-4'-yl)phenyl]-3-trifluoromethyl-5-[(3-fluoro-2'-sulfonylmethyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole trifluoroacetic acid salt



Prepared via the Stille coupling methodology using 4-tributyltinpyridine and the bromophenyl-pyrazole intermediate used in Example 8. The title compound was obtained as colorless crystals (20% yield) after purification by reverse phase HPLC. LRMS m/z (rel. intensity) 581 (M+H, 100).

Example 9

1-[3-(5-Amino-1,3,4-oxadiazol-2-yl)phenyl]-N-{2'-[(dimethylamino)methyl]-3-fluoro-1,1'-biphenyl-4-yl}-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide

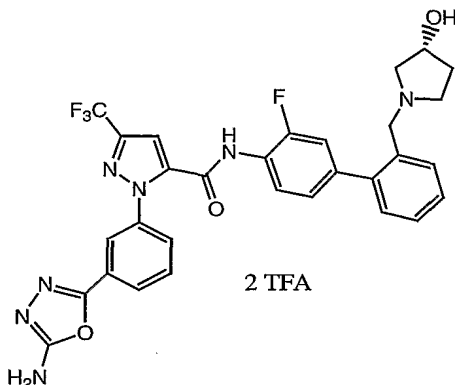


This compound was prepared by the methods described in Example 1-6. LRMS (ES^+), 566.2 ($\text{M}+\text{H}$) $^+$.

5

Example 10

1-[3-(5-Amino-1,3,4-oxadiazol-2-yl)phenyl]-N-(3-fluoro-2'-
 {[(3S)-3-hydroxy-1-pyrrolidinyl]methyl}-1,1'-biphenyl-4-yl)-
 3-(trifluoromethyl)-1H-pyrazole-5-carboxamide

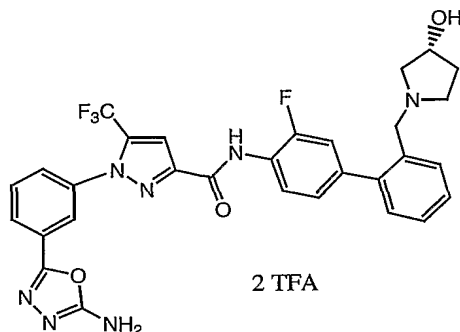


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This compound was prepared by the methods described in Example 1-6. LRMS (ES^+), 608.4 ($\text{M}+\text{H}$) $^+$.

Example 11

1-[3-(5-Amino-1,3,4-oxadiazol-2-yl)phenyl]-N-(3-fluoro-2'-
 15 {[(3S)-3-hydroxy-1-pyrrolidinyl]methyl}-1,1'-biphenyl-4-yl)-
 5-(trifluoromethyl)-1H-pyrazole-3-carboxamide



This compound was prepared by the methods described in Example 1-6. LRMS (ES⁺), 608.1 (M+H)⁺.

5 The following tables contain representative examples of the present invention. Each entry in each table is intended to be paired with each formulas at the start of the table. For example, in Tables 1 and 2, example 1 is intended to be paired with each of the formulas.

10 The following nomenclature is intended for group A in the following tables.

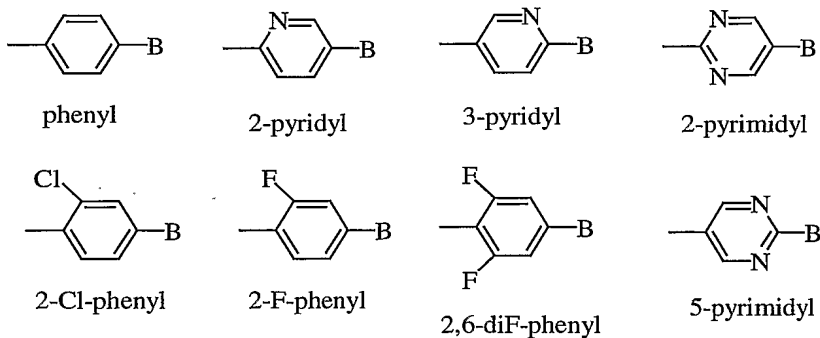
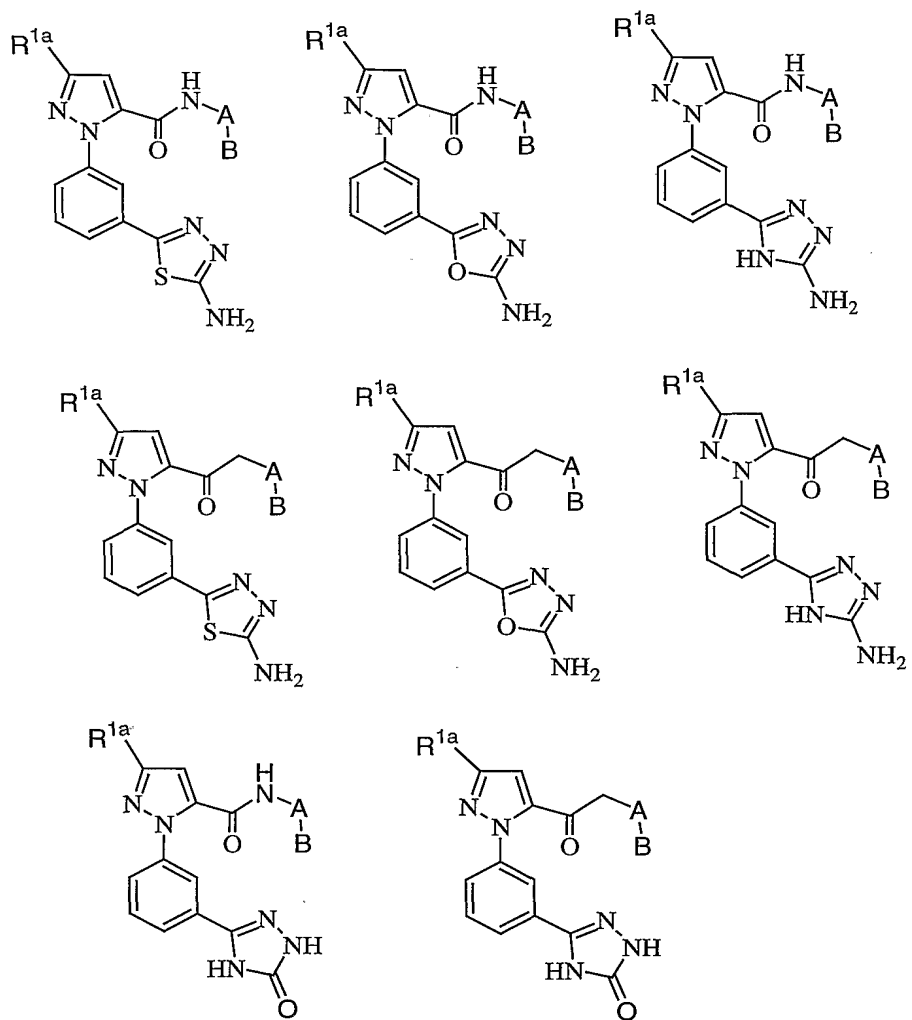
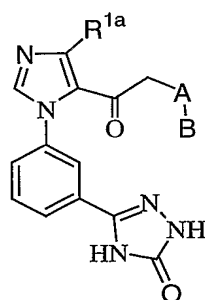
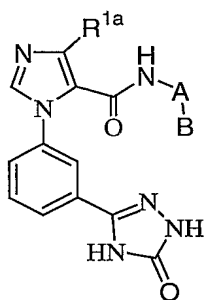
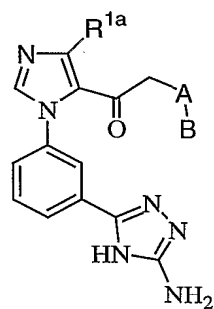
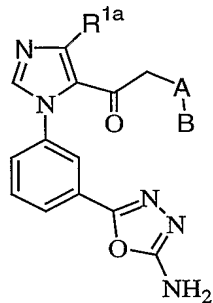
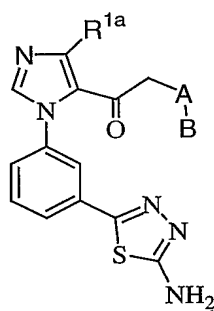
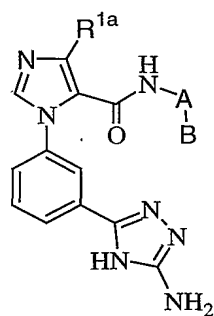
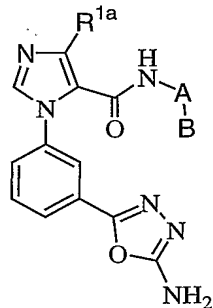
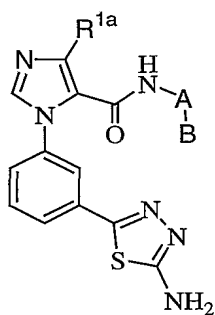
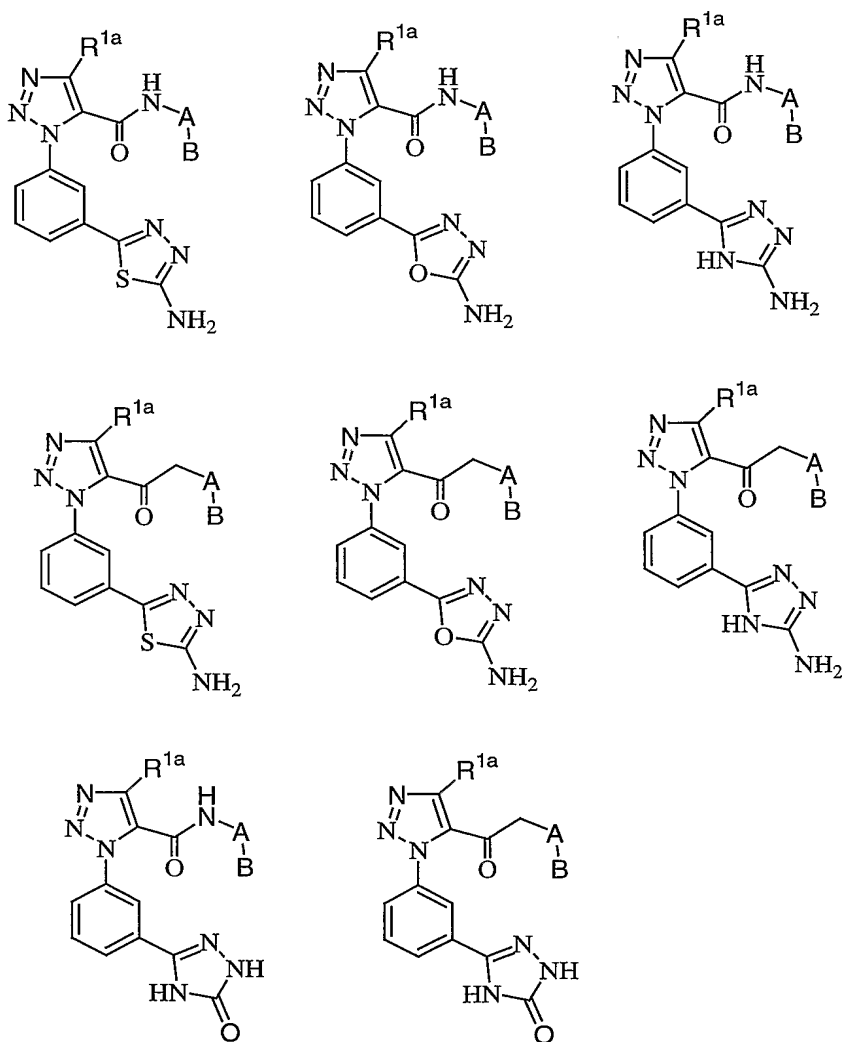
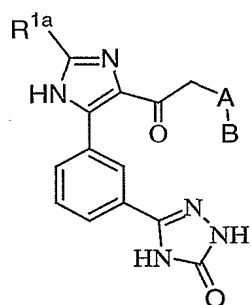
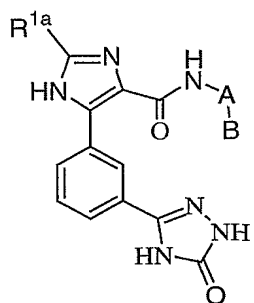
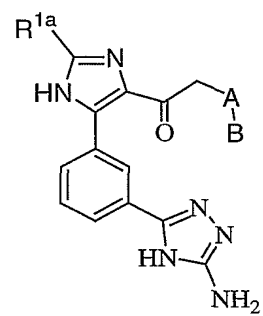
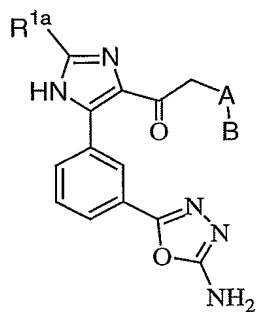
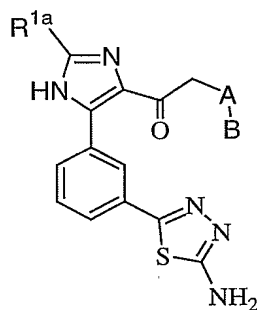
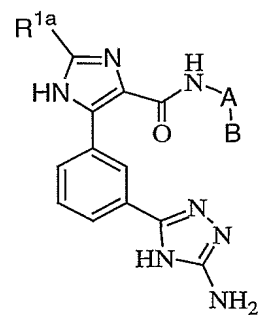
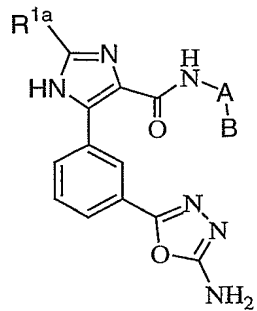
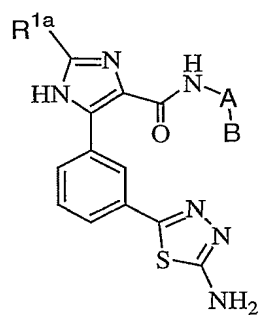


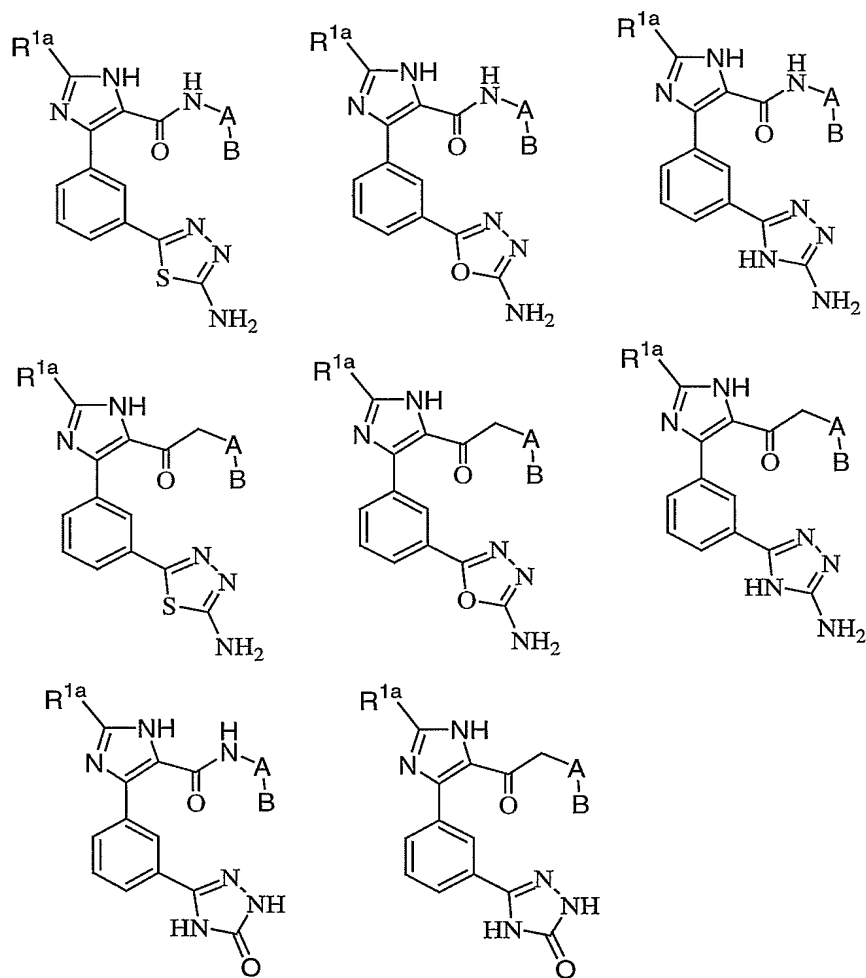
Table 1

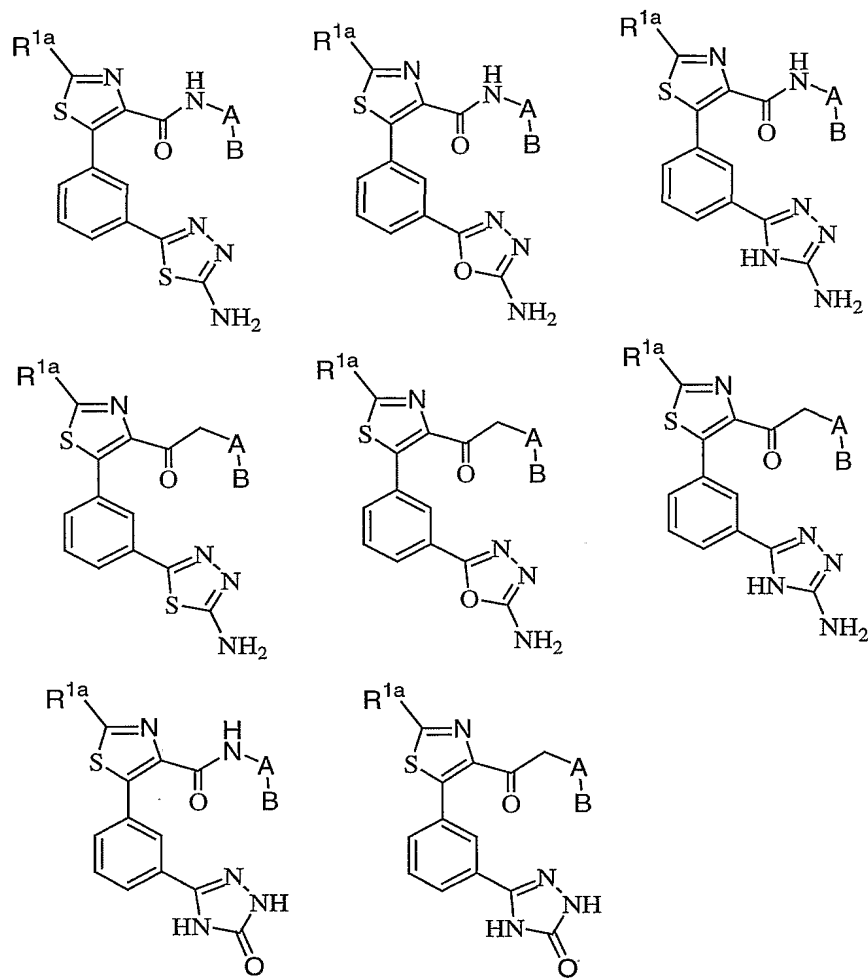


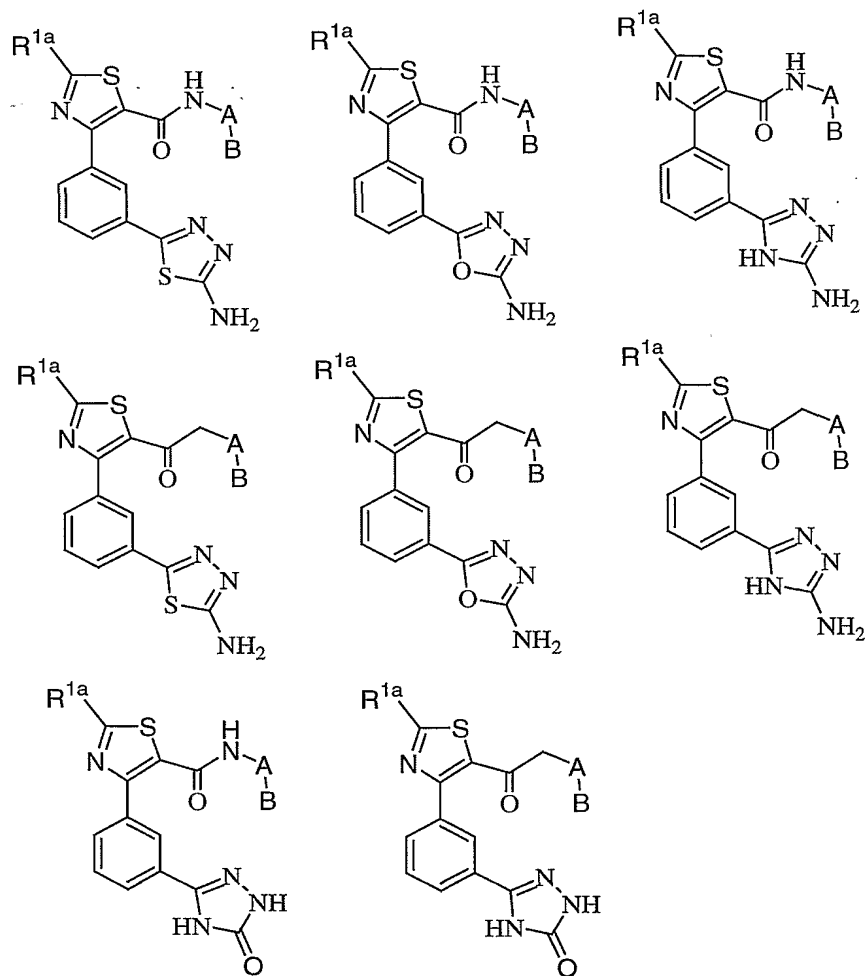












R^{1a} is CH_3 ;

	Ex#	A	B
5	1.	phenyl	2-(NH_2SO_2)phenyl
	2.	phenyl	2-(CH_3SO_2)phenyl
	3.	phenyl	3- NH_2SO_2 -4-pyridyl
	4.	phenyl	3- CH_3SO_2 -4-pyridyl
10	5.	phenyl	2-(CH_3NH)phenyl
	6.	phenyl	3-((CH_3) $_2NCH_2$)-4-pyridyl
	7.	phenyl	2-(N-(3-R-HO-pyrrolidinyl) CH_2)phenyl
	8.	phenyl	2-(N-(4-HO-piperidinyl) CH_2)phenyl
	9.	phenyl	2-((CH_3) $_2NCH_2$)phenyl
15	10.	phenyl	2-((CH_3) $NHCH_2$)phenyl
	11.	phenyl	2-((CH_3CH_2) $NHCH_2$)phenyl
	12.	phenyl	2-((CH_3CH_2) $_2NCH_2$)phenyl
	13.	phenyl	2-((CH_3CH_2) $N(CH_3)CH_2$)phenyl
	14.	phenyl	2-(((CH_3) $_2CH$) $NHCH_2$)phenyl
	15.	phenyl	2-(((CH_3) $_2CH$) $_2NCH_2$)phenyl
20	16.	phenyl	2-((cyclopropyl) $NHCH_2$)phenyl

	17.	phenyl	2-((cyclopropyl) ₂ NCH ₂)phenyl
	18.	phenyl	2-((cyclobutyl)NHCH ₂)phenyl
	19.	phenyl	2-((cyclobutyl) ₂ NCH ₂)phenyl
5	20.	phenyl	2-((cyclopentyl)NHCH ₂)phenyl
	21.	phenyl	2-((cyclopentyl) ₂ NCH ₂)phenyl
	22.	phenyl	2-((cyclohexyl)NHCH ₂)phenyl
	23.	phenyl	2-((cyclohexyl) ₂ NCH ₂)phenyl
	24.	phenyl	1-CH ₃ -2-imidazolyl
	25.	phenyl	2-CH ₃ -1-imidazolyl
10	26.	phenyl	2-((CH ₃) ₂ NCH ₂)-1-imidazolyl
	27.	phenyl	2-((CH ₃)NHCH ₂)-1-imidazolyl
	28.	phenyl	2-((CH ₃ CH ₂)NHCH ₂)-1-imidazolyl
	29.	phenyl	2-((CH ₃ CH ₂) ₂ NCH ₂)-1-imidazolyl
	30.	phenyl	2-((CH ₃ CH ₂)N(CH ₃)CH ₂)-1-imidazolyl
15	31.	phenyl	2-(((CH ₃) ₂ CH)NHCH ₂)-1-imidazolyl
	32.	phenyl	2-(((CH ₃) ₂ CH) ₂ NCH ₂)-1-imidazolyl
	33.	phenyl	2-((cyclopropyl)NHCH ₂)-1-imidazolyl
	34.	phenyl	2-((cyclopropyl) ₂ NCH ₂)-1-imidazolyl
	35.	phenyl	2-((cyclobutyl)NHCH ₂)-1-imidazolyl
20	36.	phenyl	2-((cyclobutyl) ₂ NCH ₂)-1-imidazolyl
	37.	phenyl	2-((cyclopentyl)NHCH ₂)-1-imidazolyl
	38.	phenyl	2-((cyclopentyl) ₂ NCH ₂)-1-imidazolyl
	39.	phenyl	2-((cyclohexyl)NHCH ₂)-1-imidazolyl
	40.	phenyl	2-((cyclohexyl) ₂ NCH ₂)-1-imidazolyl
25	41.	2-pyridyl	2-(NH ₂ SO ₂)phenyl
	42.	2-pyridyl	2-(CH ₃ SO ₂)phenyl
	43.	2-pyridyl	3-NH ₂ SO ₂ -4-pyridyl
	44.	2-pyridyl	3-CH ₃ SO ₂ -4-pyridyl
	45.	2-pyridyl	2-(CH ₃ NH)phenyl
30	46.	2-pyridyl	3-((CH ₃) ₂ NCH ₂)-4-pyridyl
	47.	2-pyridyl	2-(N-(3-R-HO-pyrrolidinyl)CH ₂)phenyl
	48.	2-pyridyl	2-(N-(4-HO-piperidinyl)CH ₂)phenyl
	49.	2-pyridyl	2-((CH ₃) ₂ NCH ₂)phenyl
	50.	2-pyridyl	2-((CH ₃)NHCH ₂)phenyl
35	51.	2-pyridyl	2-((CH ₃ CH ₂)NHCH ₂)phenyl
	52.	2-pyridyl	2-((CH ₃ CH ₂) ₂ NCH ₂)phenyl
	53.	2-pyridyl	2-((CH ₃ CH ₂)N(CH ₃)CH ₂)phenyl
	54.	2-pyridyl	2-(((CH ₃) ₂ CH)NHCH ₂)phenyl
	55.	2-pyridyl	2-(((CH ₃) ₂ CH) ₂ NCH ₂)phenyl
40	56.	2-pyridyl	2-((cyclopropyl)NHCH ₂)phenyl
	57.	2-pyridyl	2-((cyclopropyl) ₂ NCH ₂)phenyl
	58.	2-pyridyl	2-((cyclobutyl)NHCH ₂)phenyl
	59.	2-pyridyl	2-((cyclobutyl) ₂ NCH ₂)phenyl
	60.	2-pyridyl	2-((cyclopentyl)NHCH ₂)phenyl
45	61.	2-pyridyl	2-((cyclopentyl) ₂ NCH ₂)phenyl
	62.	2-pyridyl	2-((cyclohexyl)NHCH ₂)phenyl
	63.	2-pyridyl	2-((cyclohexyl) ₂ NCH ₂)phenyl
	64.	2-pyridyl	1-CH ₃ -2-imidazolyl
	65.	2-pyridyl	2-CH ₃ -1-imidazolyl
50	66.	2-pyridyl	2-((CH ₃) ₂ NCH ₂)-1-imidazolyl
	67.	2-pyridyl	2-((CH ₃)NHCH ₂)-1-imidazolyl
	68.	2-pyridyl	2-((CH ₃ CH ₂)NHCH ₂)-1-imidazolyl
	69.	2-pyridyl	2-((CH ₃ CH ₂) ₂ NCH ₂)-1-imidazolyl

	70.	2-pyridyl	2-((CH ₃ CH ₂)N(CH ₃)CH ₂)-1-imidazolyl
	71.	2-pyridyl	2-(((CH ₃) ₂ CH)NHCH ₂)-1-imidazolyl
	72.	2-pyridyl	2-(((CH ₃) ₂ CH) ₂ NCH ₂)-1-imidazolyl
	73.	2-pyridyl	2-((cyclopropyl)NHCH ₂)-1-imidazolyl
5	74.	2-pyridyl	2-((cyclopropyl) ₂ NCH ₂)-1-imidazolyl
	75.	2-pyridyl	2-((cyclobutyl)NHCH ₂)-1-imidazolyl
	76.	2-pyridyl	2-((cyclobutyl) ₂ NCH ₂)-1-imidazolyl
	77.	2-pyridyl	2-((cyclopentyl)NHCH ₂)-1-imidazolyl
	78.	2-pyridyl	2-((cyclopentyl) ₂ NCH ₂)-1-imidazolyl
10	79.	2-pyridyl	2-((cyclohexyl)NHCH ₂)-1-imidazolyl
	80.	2-pyridyl	2-((cyclohexyl) ₂ NCH ₂)-1-imidazolyl
	81.	3-pyridyl	2-(NH ₂ SO ₂)phenyl
	82.	3-pyridyl	2-(CH ₃ SO ₂)phenyl
	83.	3-pyridyl	3-NH ₂ SO ₂ -4-pyridyl
15	84.	3-pyridyl	3-CH ₃ SO ₂ -4-pyridyl
	85.	3-pyridyl	2-(CH ₃ NH)phenyl
	86.	3-pyridyl	3-((CH ₃) ₂ NCH ₂)-4-pyridyl
	87.	3-pyridyl	2-(N-(3-R-HO-pyrrolidinyl)CH ₂)phenyl
	88.	3-pyridyl	2-(N-(4-HO-piperidinyl)CH ₂)phenyl
20	89.	3-pyridyl	2-((CH ₃) ₂ NCH ₂)phenyl
	90.	3-pyridyl	2-((CH ₃)NHCH ₂)phenyl
	91.	3-pyridyl	2-((CH ₃ CH ₂)NHCH ₂)phenyl
	92.	3-pyridyl	2-((CH ₃ CH ₂) ₂ NCH ₂)phenyl
	93.	3-pyridyl	2-((CH ₃ CH ₂)N(CH ₃)CH ₂)phenyl
25	94.	3-pyridyl	2-(((CH ₃) ₂ CH)NHCH ₂)phenyl
	95.	3-pyridyl	2-(((CH ₃) ₂ CH) ₂ NCH ₂)phenyl
	96.	3-pyridyl	2-((cyclopropyl)NHCH ₂)phenyl
	97.	3-pyridyl	2-((cyclopropyl) ₂ NCH ₂)phenyl
	98.	3-pyridyl	2-((cyclobutyl)NHCH ₂)phenyl
30	99.	3-pyridyl	2-((cyclobutyl) ₂ NCH ₂)phenyl
	100.	3-pyridyl	2-((cyclopentyl)NHCH ₂)phenyl
	101.	3-pyridyl	2-((cyclopentyl) ₂ NCH ₂)phenyl
	102.	3-pyridyl	2-((cyclohexyl)NHCH ₂)phenyl
	103.	3-pyridyl	2-((cyclohexyl) ₂ NCH ₂)phenyl
35	104.	3-pyridyl	1-CH ₃ -2-imidazolyl
	105.	3-pyridyl	2-CH ₃ -1-imidazolyl
	106.	3-pyridyl	2-((CH ₃) ₂ NCH ₂)-1-imidazolyl
	107.	3-pyridyl	2-((CH ₃)NHCH ₂)-1-imidazolyl
	108.	3-pyridyl	2-((CH ₃ CH ₂)NHCH ₂)-1-imidazolyl
40	109.	3-pyridyl	2-((CH ₃ CH ₂) ₂ NCH ₂)-1-imidazolyl
	110.	3-pyridyl	2-((CH ₃ CH ₂)N(CH ₃)CH ₂)-1-imidazolyl
	111.	3-pyridyl	2-(((CH ₃) ₂ CH)NHCH ₂)-1-imidazolyl
	112.	3-pyridyl	2-(((CH ₃) ₂ CH) ₂ NCH ₂)-1-imidazolyl
	113.	3-pyridyl	2-((cyclopropyl)NHCH ₂)-1-imidazolyl
45	114.	3-pyridyl	2-((cyclopropyl) ₂ NCH ₂)-1-imidazolyl
	115.	3-pyridyl	2-((cyclobutyl)NHCH ₂)-1-imidazolyl
	116.	3-pyridyl	2-((cyclobutyl) ₂ NCH ₂)-1-imidazolyl
	117.	3-pyridyl	2-((cyclopentyl)NHCH ₂)-1-imidazolyl
	118.	3-pyridyl	2-((cyclopentyl) ₂ NCH ₂)-1-imidazolyl
50	119.	3-pyridyl	2-((cyclohexyl)NHCH ₂)-1-imidazolyl
	120.	3-pyridyl	2-((cyclohexyl) ₂ NCH ₂)-1-imidazolyl
	121.	2-pyrimidyl	2-(NH ₂ SO ₂)phenyl
	122.	2-pyrimidyl	2-(CH ₃ SO ₂)phenyl

	123.	2-pyrimidyl	3-NH ₂ SO ₂ -4-pyridyl
	124.	2-pyrimidyl	3-CH ₃ SO ₂ -4-pyridyl
	125.	2-pyrimidyl	2-(CH ₃ NH)phenyl
	126.	2-pyrimidyl	3-((CH ₃) ₂ NCH ₂)-4-pyridyl
5	127.	2-pyrimidyl	2-(N-(3-R-HO-pyrrolidinyl)CH ₂)phenyl
	128.	2-pyrimidyl	2-(N-(4-HO-piperidinyl)CH ₂)phenyl
	129.	2-pyrimidyl	2-((CH ₃) ₂ NCH ₂)phenyl
	130.	2-pyrimidyl	2-((CH ₃)NHCH ₂)phenyl
	131.	2-pyrimidyl	2-((CH ₃ CH ₂)NHCH ₂)phenyl
10	132.	2-pyrimidyl	2-((CH ₃ CH ₂) ₂ NCH ₂)phenyl
	133.	2-pyrimidyl	2-((CH ₃ CH ₂)N(CH ₃)CH ₂)phenyl
	134.	2-pyrimidyl	2-(((CH ₃) ₂ CH)NHCH ₂)phenyl
	135.	2-pyrimidyl	2-(((CH ₃) ₂ CH) ₂ NCH ₂)phenyl
	136.	2-pyrimidyl	2-((cyclopropyl)NHCH ₂)phenyl
15	137.	2-pyrimidyl	2-((cyclopropyl) ₂ NCH ₂)phenyl
	138.	2-pyrimidyl	2-((cyclobutyl)NHCH ₂)phenyl
	139.	2-pyrimidyl	2-((cyclobutyl) ₂ NCH ₂)phenyl
	140.	2-pyrimidyl	2-((cyclopentyl)NHCH ₂)phenyl
	141.	2-pyrimidyl	2-((cyclopentyl) ₂ NCH ₂)phenyl
20	142.	2-pyrimidyl	2-((cyclohexyl)NHCH ₂)phenyl
	143.	2-pyrimidyl	2-((cyclohexyl) ₂ NCH ₂)phenyl
	144.	2-pyrimidyl	1-CH ₃ -2-imidazolyl
	145.	2-pyrimidyl	2-CH ₃ -1-imidazolyl
	146.	2-pyrimidyl	2-((CH ₃) ₂ NCH ₂)-1-imidazolyl
25	147.	2-pyrimidyl	2-((CH ₃)NHCH ₂)-1-imidazolyl
	148.	2-pyrimidyl	2-((CH ₃ CH ₂)NHCH ₂)-1-imidazolyl
	149.	2-pyrimidyl	2-((CH ₃ CH ₂) ₂ NCH ₂)-1-imidazolyl
	150.	2-pyrimidyl	2-((CH ₃ CH ₂)N(CH ₃)CH ₂)-1-imidazolyl
	151.	2-pyrimidyl	2-(((CH ₃) ₂ CH)NHCH ₂)-1-imidazolyl
30	152.	2-pyrimidyl	2-(((CH ₃) ₂ CH) ₂ NCH ₂)-1-imidazolyl
	153.	2-pyrimidyl	2-((cyclopropyl)NHCH ₂)-1-imidazolyl
	154.	2-pyrimidyl	2-((cyclopropyl) ₂ NCH ₂)-1-imidazolyl
	155.	2-pyrimidyl	2-((cyclobutyl)NHCH ₂)-1-imidazolyl
	156.	2-pyrimidyl	2-((cyclobutyl) ₂ NCH ₂)-1-imidazolyl
35	157.	2-pyrimidyl	2-((cyclopentyl)NHCH ₂)-1-imidazolyl
	158.	2-pyrimidyl	2-((cyclopentyl) ₂ NCH ₂)-1-imidazolyl
	159.	2-pyrimidyl	2-((cyclohexyl)NHCH ₂)-1-imidazolyl
	160.	2-pyrimidyl	2-((cyclohexyl) ₂ NCH ₂)-1-imidazolyl
	161.	5-pyrimidyl	2-(NH ₂ SO ₂)phenyl
40	162.	5-pyrimidyl	2-(CH ₃ SO ₂)phenyl
	163.	5-pyrimidyl	3-NH ₂ SO ₂ -4-pyridyl
	164.	5-pyrimidyl	3-CH ₃ SO ₂ -4-pyridyl
	165.	5-pyrimidyl	2-(CH ₃ NH)phenyl
	166.	5-pyrimidyl	3-((CH ₃) ₂ NCH ₂)-4-pyridyl
45	167.	5-pyrimidyl	2-(N-(3-R-HO-pyrrolidinyl)CH ₂)phenyl
	168.	5-pyrimidyl	2-(N-(4-HO-piperidinyl)CH ₂)phenyl
	169.	5-pyrimidyl	2-((CH ₃) ₂ NCH ₂)phenyl
	170.	5-pyrimidyl	2-((CH ₃)NHCH ₂)phenyl
	171.	5-pyrimidyl	2-((CH ₃ CH ₂)NHCH ₂)phenyl
50	172.	5-pyrimidyl	2-((CH ₃ CH ₂) ₂ NCH ₂)phenyl
	173.	5-pyrimidyl	2-((CH ₃ CH ₂)N(CH ₃)CH ₂)phenyl
	174.	5-pyrimidyl	2-(((CH ₃) ₂ CH)NHCH ₂)phenyl
	175.	5-pyrimidyl	2-(((CH ₃) ₂ CH) ₂ NCH ₂)phenyl

	176.	5-pyrimidyl	2-((cyclopropyl)NHCH ₂)phenyl
	177.	5-pyrimidyl	2-((cyclopropyl) ₂ NCH ₂)phenyl
	178.	5-pyrimidyl	2-((cyclobutyl)NHCH ₂)phenyl
	179.	5-pyrimidyl	2-((cyclobutyl) ₂ NCH ₂)phenyl
5	180.	5-pyrimidyl	2-((cyclopentyl)NHCH ₂)phenyl
	181.	5-pyrimidyl	2-((cyclopentyl) ₂ NCH ₂)phenyl
	182.	5-pyrimidyl	2-((cyclohexyl)NHCH ₂)phenyl
	183.	5-pyrimidyl	2-((cyclohexyl) ₂ NCH ₂)phenyl
	184.	5-pyrimidyl	1-CH ₃ -2-imidazolyl
10	185.	5-pyrimidyl	2-CH ₃ -1-imidazolyl
	186.	5-pyrimidyl	2-((CH ₃) ₂ NCH ₂)-1-imidazolyl
	187.	5-pyrimidyl	2-((CH ₃)NHCH ₂)-1-imidazolyl
	188.	5-pyrimidyl	2-((CH ₃ CH ₂)NHCH ₂)-1-imidazolyl
	189.	5-pyrimidyl	2-((CH ₃ CH ₂) ₂ NCH ₂)-1-imidazolyl
15	190.	5-pyrimidyl	2-((CH ₃ CH ₂)N(CH ₃)CH ₂)-1-imidazolyl
	191.	5-pyrimidyl	2-(((CH ₃) ₂ CH)NHCH ₂)-1-imidazolyl
	192.	5-pyrimidyl	2-(((CH ₃) ₂ CH) ₂ NCH ₂)-1-imidazolyl
	193.	5-pyrimidyl	2-((cyclopropyl)NHCH ₂)-1-imidazolyl
	194.	5-pyrimidyl	2-((cyclopropyl) ₂ NCH ₂)-1-imidazolyl
20	195.	5-pyrimidyl	2-((cyclobutyl)NHCH ₂)-1-imidazolyl
	196.	5-pyrimidyl	2-((cyclobutyl) ₂ NCH ₂)-1-imidazolyl
	197.	5-pyrimidyl	2-((cyclopentyl)NHCH ₂)-1-imidazolyl
	198.	5-pyrimidyl	2-((cyclopentyl) ₂ NCH ₂)-1-imidazolyl
	199.	5-pyrimidyl	2-((cyclohexyl)NHCH ₂)-1-imidazolyl
25	200.	5-pyrimidyl	2-((cyclohexyl) ₂ NCH ₂)-1-imidazolyl
	201.	2-Cl-phenyl	2-(NH ₂ SO ₂)phenyl
	202.	2-Cl-phenyl	2-(CH ₃ SO ₂)phenyl
	203.	2-Cl-phenyl	3-NH ₂ SO ₂ -4-pyridyl
	204.	2-Cl-phenyl	3-CH ₃ SO ₂ -4-pyridyl
30	205.	2-Cl-phenyl	2-(CH ₃ NH)phenyl
	206.	2-Cl-phenyl	3-((CH ₃) ₂ NCH ₂)-4-pyridyl
	207.	2-Cl-phenyl	2-(N-(3-R-HO-pyrrolidinyl)CH ₂)phenyl
	208.	2-Cl-phenyl	2-(N-(4-HO-piperidinyl)CH ₂)phenyl
	209.	2-Cl-phenyl	2-((CH ₃) ₂ NCH ₂)phenyl
35	210.	2-Cl-phenyl	2-((CH ₃)NHCH ₂)phenyl
	211.	2-Cl-phenyl	2-((CH ₃ CH ₂)NHCH ₂)phenyl
	212.	2-Cl-phenyl	2-((CH ₃ CH ₂) ₂ NCH ₂)phenyl
	213.	2-Cl-phenyl	2-((CH ₃ CH ₂)N(CH ₃)CH ₂)phenyl
	214.	2-Cl-phenyl	2-(((CH ₃) ₂ CH)NHCH ₂)phenyl
40	215.	2-Cl-phenyl	2-(((CH ₃) ₂ CH) ₂ NCH ₂)phenyl
	216.	2-Cl-phenyl	2-((cyclopropyl)NHCH ₂)phenyl
	217.	2-Cl-phenyl	2-((cyclopropyl) ₂ NCH ₂)phenyl
	218.	2-Cl-phenyl	2-((cyclobutyl)NHCH ₂)phenyl
	219.	2-Cl-phenyl	2-((cyclobutyl) ₂ NCH ₂)phenyl
45	220.	2-Cl-phenyl	2-((cyclopentyl)NHCH ₂)phenyl
	221.	2-Cl-phenyl	2-((cyclopentyl) ₂ NCH ₂)phenyl
	222.	2-Cl-phenyl	2-((cyclohexyl)NHCH ₂)phenyl
	223.	2-Cl-phenyl	2-((cyclohexyl) ₂ NCH ₂)phenyl
	224.	2-Cl-phenyl	1-CH ₃ -2-imidazolyl
50	225.	2-Cl-phenyl	2-CH ₃ -1-imidazolyl
	226.	2-Cl-phenyl	2-((CH ₃) ₂ NCH ₂)-1-imidazolyl
	227.	2-Cl-phenyl	2-((CH ₃)NHCH ₂)-1-imidazolyl
	228.	2-Cl-phenyl	2-((CH ₃ CH ₂)NHCH ₂)-1-imidazolyl

	229.	2-Cl-phenyl	2-((CH ₃ CH ₂) ₂ NCH ₂)-1-imidazolyl
	230.	2-Cl-phenyl	2-((CH ₃ CH ₂)N(CH ₃)CH ₂)-1-imidazolyl
	231.	2-Cl-phenyl	2-(((CH ₃) ₂ CH)NHCH ₂)-1-imidazolyl
	232.	2-Cl-phenyl	2-(((CH ₃) ₂ CH) ₂ NCH ₂)-1-imidazolyl
5	233.	2-Cl-phenyl	2-((cyclopropyl)NHCH ₂)-1-imidazolyl
	234.	2-Cl-phenyl	2-((cyclopropyl) ₂ NCH ₂)-1-imidazolyl
	235.	2-Cl-phenyl	2-((cyclobutyl)NHCH ₂)-1-imidazolyl
	236.	2-Cl-phenyl	2-((cyclobutyl) ₂ NCH ₂)-1-imidazolyl
	237.	2-Cl-phenyl	2-((cyclopentyl)NHCH ₂)-1-imidazolyl
10	238.	2-Cl-phenyl	2-((cyclopentyl) ₂ NCH ₂)-1-imidazolyl
	239.	2-Cl-phenyl	2-((cyclohexyl)NHCH ₂)-1-imidazolyl
	240.	2-Cl-phenyl	2-((cyclohexyl) ₂ NCH ₂)-1-imidazolyl
	241.	2-F-phenyl	2-(NH ₂ SO ₂)phenyl
	242.	2-F-phenyl	2-(CH ₃ SO ₂)phenyl
15	243.	2-F-phenyl	3-NH ₂ SO ₂ -4-pyridyl
	244.	2-F-phenyl	3-CH ₃ SO ₂ -4-pyridyl
	245.	2-F-phenyl	2-(CH ₃ NH)phenyl
	246.	2-F-phenyl	3-((CH ₃) ₂ NCH ₂)-4-pyridyl
	247.	2-F-phenyl	2-(N-(3-R-HO-pyrrolidinyl)CH ₂)phenyl
20	248.	2-F-phenyl	2-(N-(4-HO-piperidinyl)CH ₂)phenyl
	249.	2-F-phenyl	2-((CH ₃) ₂ NCH ₂)phenyl
	250.	2-F-phenyl	2-((CH ₃)NHCH ₂)phenyl
	251.	2-F-phenyl	2-((CH ₃ CH ₂)NHCH ₂)phenyl
	252.	2-F-phenyl	2-((CH ₃ CH ₂) ₂ NCH ₂)phenyl
25	253.	2-F-phenyl	2-((CH ₃ CH ₂)N(CH ₃)CH ₂)phenyl
	254.	2-F-phenyl	2-(((CH ₃) ₂ CH)NHCH ₂)phenyl
	255.	2-F-phenyl	2-(((CH ₃) ₂ CH) ₂ NCH ₂)phenyl
	256.	2-F-phenyl	2-((cyclopropyl)NHCH ₂)phenyl
	257.	2-F-phenyl	2-((cyclopropyl) ₂ NCH ₂)phenyl
30	258.	2-F-phenyl	2-((cyclobutyl)NHCH ₂)phenyl
	259.	2-F-phenyl	2-((cyclobutyl) ₂ NCH ₂)phenyl
	260.	2-F-phenyl	2-((cyclopentyl)NHCH ₂)phenyl
	261.	2-F-phenyl	2-((cyclopentyl) ₂ NCH ₂)phenyl
	262.	2-F-phenyl	2-((cyclohexyl)NHCH ₂)phenyl
35	263.	2-F-phenyl	2-((cyclohexyl) ₂ NCH ₂)phenyl
	264.	2-F-phenyl	1-CH ₃ -2-imidazolyl
	265.	2-F-phenyl	2-CH ₃ -1-imidazolyl
	266.	2-F-phenyl	2-((CH ₃) ₂ NCH ₂)-1-imidazolyl
	267.	2-F-phenyl	2-((CH ₃)NHCH ₂)-1-imidazolyl
40	268.	2-F-phenyl	2-((CH ₃ CH ₂)NHCH ₂)-1-imidazolyl
	269.	2-F-phenyl	2-((CH ₃ CH ₂) ₂ NCH ₂)-1-imidazolyl
	270.	2-F-phenyl	2-((CH ₃ CH ₂)N(CH ₃)CH ₂)-1-imidazolyl
	271.	2-F-phenyl	2-(((CH ₃) ₂ CH)NHCH ₂)-1-imidazolyl
	272.	2-F-phenyl	2-(((CH ₃) ₂ CH) ₂ NCH ₂)-1-imidazolyl
45	273.	2-F-phenyl	2-((cyclopropyl)NHCH ₂)-1-imidazolyl
	274.	2-F-phenyl	2-((cyclopropyl) ₂ NCH ₂)-1-imidazolyl
	275.	2-F-phenyl	2-((cyclobutyl)NHCH ₂)-1-imidazolyl
	276.	2-F-phenyl	2-((cyclobutyl) ₂ NCH ₂)-1-imidazolyl
	277.	2-F-phenyl	2-((cyclopentyl)NHCH ₂)-1-imidazolyl
50	278.	2-F-phenyl	2-((cyclopentyl) ₂ NCH ₂)-1-imidazolyl
	279.	2-F-phenyl	2-((cyclohexyl)NHCH ₂)-1-imidazolyl
	280.	2-F-phenyl	2-((cyclohexyl) ₂ NCH ₂)-1-imidazolyl
	281.	2,6-diF-phenyl	2-(NH ₂ SO ₂)phenyl

	282.	2,6-diF-phenyl	2-(CH ₃ SO ₂)phenyl
	283.	2,6-diF-phenyl	3-NH ₂ SO ₂ -4-pyridyl
	284.	2,6-diF-phenyl	3-CH ₃ SO ₂ -4-pyridyl
5	285.	2,6-diF-phenyl	2-(CH ₃ NH)phenyl
	286.	2,6-diF-phenyl	3-((CH ₃) ₂ NCH ₂)-4-pyridyl
	287.	2,6-diF-phenyl	2-(N-(3-R-HO-pyrrolidinyl)CH ₂)phenyl
	288.	2,6-diF-phenyl	2-(N-(4-HO-piperidinyl)CH ₂)phenyl
	289.	2,6-diF-phenyl	2-((CH ₃) ₂ NCH ₂)phenyl
10	290.	2,6-diF-phenyl	2-((CH ₃)NHCH ₂)phenyl
	291.	2,6-diF-phenyl	2-((CH ₃ CH ₂)NHCH ₂)phenyl
	292.	2,6-diF-phenyl	2-((CH ₃ CH ₂) ₂ NCH ₂)phenyl
	293.	2,6-diF-phenyl	2-((CH ₃ CH ₂)N(CH ₃)CH ₂)phenyl
	294.	2,6-diF-phenyl	2-(((CH ₃) ₂ CH)NHCH ₂)phenyl
	295.	2,6-diF-phenyl	2-(((CH ₃) ₂ CH) ₂ NCH ₂)phenyl
15	296.	2,6-diF-phenyl	2-((cyclopropyl)NHCH ₂)phenyl
	297.	2,6-diF-phenyl	2-((cyclopropyl) ₂ NCH ₂)phenyl
	298.	2,6-diF-phenyl	2-((cyclobutyl)NHCH ₂)phenyl
	299.	2,6-diF-phenyl	2-((cyclobutyl) ₂ NCH ₂)phenyl
	300.	2,6-diF-phenyl	2-((cyclopentyl)NHCH ₂)phenyl
20	301.	2,6-diF-phenyl	2-((cyclopentyl) ₂ NCH ₂)phenyl
	302.	2,6-diF-phenyl	2-((cyclohexyl)NHCH ₂)phenyl
	303.	2,6-diF-phenyl	2-((cyclohexyl) ₂ NCH ₂)phenyl
	304.	2,6-diF-phenyl	1-CH ₃ -2-imidazolyl
	305.	2,6-diF-phenyl	2-CH ₃ -1-imidazolyl
25	306.	2,6-diF-phenyl	2-((CH ₃) ₂ NCH ₂)-1-imidazolyl
	307.	2,6-diF-phenyl	2-((CH ₃)NHCH ₂)-1-imidazolyl
	308.	2,6-diF-phenyl	2-((CH ₃ CH ₂)NHCH ₂)-1-imidazolyl
	309.	2,6-diF-phenyl	2-((CH ₃ CH ₂) ₂ NCH ₂)-1-imidazolyl
	310.	2,6-diF-phenyl	2-((CH ₃ CH ₂)N(CH ₃)CH ₂)-1-imidazolyl
30	311.	2,6-diF-phenyl	2-(((CH ₃) ₂ CH)NHCH ₂)-1-imidazolyl
	312.	2,6-diF-phenyl	2-(((CH ₃) ₂ CH) ₂ NCH ₂)-1-imidazolyl
	313.	2,6-diF-phenyl	2-((cyclopropyl)NHCH ₂)-1-imidazolyl
	314.	2,6-diF-phenyl	2-((cyclopropyl) ₂ NCH ₂)-1-imidazolyl
	315.	2,6-diF-phenyl	2-((cyclobutyl)NHCH ₂)-1-imidazolyl
35	316.	2,6-diF-phenyl	2-((cyclobutyl) ₂ NCH ₂)-1-imidazolyl
	317.	2,6-diF-phenyl	2-((cyclopentyl)NHCH ₂)-1-imidazolyl
	318.	2,6-diF-phenyl	2-((cyclopentyl) ₂ NCH ₂)-1-imidazolyl
	319.	2,6-diF-phenyl	2-((cyclohexyl)NHCH ₂)-1-imidazolyl
	320.	2,6-diF-phenyl	2-((cyclohexyl) ₂ NCH ₂)-1-imidazolyl
40	321.	piperidinyl	2-(NH ₂ SO ₂)phenyl
	322.	piperidinyl	2-(CH ₃ SO ₂)phenyl
	323.	piperidinyl	3-NH ₂ SO ₂ -4-pyridyl
	324.	piperidinyl	3-CH ₃ SO ₂ -4-pyridyl
	325.	piperidinyl	2-(CH ₃ NH)phenyl
45	326.	piperidinyl	3-((CH ₃) ₂ NCH ₂)-4-pyridyl
	327.	piperidinyl	2-(N-(3-R-HO-pyrrolidinyl)CH ₂)phenyl
	328.	piperidinyl	2-(N-(4-HO-piperidinyl)CH ₂)phenyl
	329.	piperidinyl	2-((CH ₃) ₂ NCH ₂)phenyl
	330.	piperidinyl	2-((CH ₃)NHCH ₂)phenyl
50	331.	piperidinyl	2-((CH ₃ CH ₂)NHCH ₂)phenyl
	332.	piperidinyl	2-((CH ₃ CH ₂) ₂ NCH ₂)phenyl
	333.	piperidinyl	2-((CH ₃ CH ₂)N(CH ₃)CH ₂)phenyl
	334.	piperidinyl	2-(((CH ₃) ₂ CH)NHCH ₂)phenyl

	335.	piperidiny1	2-(((CH ₃) ₂ CH) ₂ NCH ₂)phenyl
	336.	piperidiny1	2-((cyclopropyl)NHCH ₂)phenyl
	337.	piperidiny1	2-((cyclopropyl) ₂ NCH ₂)phenyl
	338.	piperidiny1	2-((cyclobutyl)NHCH ₂)phenyl
5	339.	piperidiny1	2-((cyclobutyl) ₂ NCH ₂)phenyl
	340.	piperidiny1	2-((cyclopentyl)NHCH ₂)phenyl
	341.	piperidiny1	2-((cyclopentyl) ₂ NCH ₂)phenyl
	342.	piperidiny1	2-((cyclohexyl)NHCH ₂)phenyl
	343.	piperidiny1	2-((cyclohexyl) ₂ NCH ₂)phenyl
10	344.	piperidiny1	1-CH ₃ -2-imidazolyl
	345.	piperidiny1	2-CH ₃ -1-imidazolyl
	346.	piperidiny1	2-((CH ₃) ₂ NCH ₂)-1-imidazolyl
	347.	piperidiny1	2-((CH ₃)NHCH ₂)-1-imidazolyl
	348.	piperidiny1	2-((CH ₃ CH ₂)NHCH ₂)-1-imidazolyl
15	349.	piperidiny1	2-((CH ₃ CH ₂) ₂ NCH ₂)-1-imidazolyl
	350.	piperidiny1	2-((CH ₃ CH ₂)N(CH ₃)CH ₂)-1-imidazolyl
	351.	piperidiny1	2-(((CH ₃) ₂ CH)NHCH ₂)-1-imidazolyl
	352.	piperidiny1	2-(((CH ₃) ₂ CH) ₂ NCH ₂)-1-imidazolyl
	353.	piperidiny1	2-((cyclopropyl)NHCH ₂)-1-imidazolyl
20	354.	piperidiny1	2-((cyclopropyl) ₂ NCH ₂)-1-imidazolyl
	355.	piperidiny1	2-((cyclobutyl)NHCH ₂)-1-imidazolyl
	356.	piperidiny1	2-((cyclobutyl) ₂ NCH ₂)-1-imidazolyl
	357.	piperidiny1	2-((cyclopentyl)NHCH ₂)-1-imidazolyl
	358.	piperidiny1	2-((cyclopentyl) ₂ NCH ₂)-1-imidazolyl
25	359.	piperidiny1	2-((cyclohexyl)NHCH ₂)-1-imidazolyl
	360.	piperidiny1	2-((cyclohexyl) ₂ NCH ₂)-1-imidazolyl
30			

Table 2

Examples -360 use the structures from Table 1 and the corresponding A and B groups from Examples -360 of Table 1, and:

5 R^{1a} is CH_2CH_3 .

Table 3

Examples -360 use the structures from Table 1 and the corresponding A and B groups from Examples -360 of Table 1, and:

10 R^{1a} is CF_3 .

Table 4

Examples -360 use the structures from Table 1 and the corresponding A and B groups from Examples -360 of Table 1, and:

15 R^{1a} is SCH_3 .

Table 5

Examples -360 use the structures from Table 1 and the corresponding A and B groups from Examples -360 of Table 1, and:

20 R^{1a} is SOCH_3 .

Table 6

Examples -360 use the structures from Table 1 and the corresponding A and B groups from Examples -360 of Table 1, and:

25 R^{1a} is SO_2CH_3 .

Table 7

Examples -360 use the structures from Table 1 and the corresponding A and B groups from Examples -360 of Table 1, and:

30 R^{1a} is Cl .

Table 8

Examples -360 use the structures from Table 1 and the corresponding A and B groups from Examples -360 of Table 1, and:

R^{1a} is F.

Table 9

Examples -360 use the structures from Table 1 and the corresponding A and B groups from Examples -360 of Table 1, and:

R^{1a} is CO_2CH_3 .

Table 10

Examples -360 use the structures from Table 1 and the corresponding A and B groups from Examples -360 of Table 1, and:

R^{1a} is CH_2OCH_3 .

Table 11

Examples -360 use the structures from Table 1 and the corresponding A and B groups from Examples -360 of Table 1, and:

R^{1a} is CONH_2 .

Table 12

Examples -360 use the structures from Table 1 and the corresponding A and B groups from Examples -360 of Table 1, and:

R^{1a} is CN.

Table 13

Examples -360 use the structures from Table 1 and the corresponding A and B groups from Examples -360 of Table 1, and:

R^{1a} is CH₂NH₂.

Table 14

5 Examples -360 use the structures from Table 1 and the corresponding A and B groups from Examples -360 of Table 1, and:

R^{1a} is CH₂NHSO₂CH₃.

Table 15

10 Examples -360 use the structures from Table 1 and the corresponding A and B groups from Examples -360 of Table 1, and:

R^{1a} is 1-imidazolyl-CH₂.

15

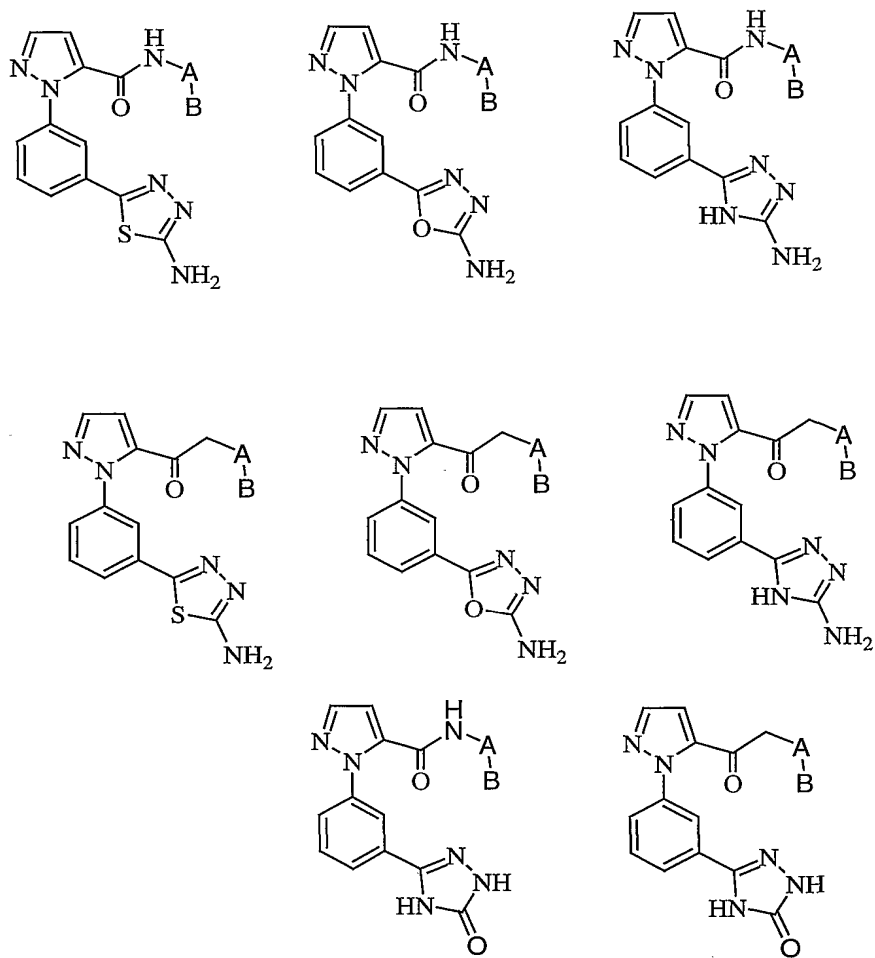
Table 16

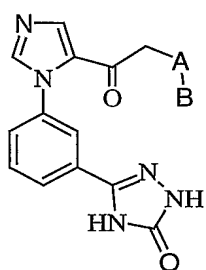
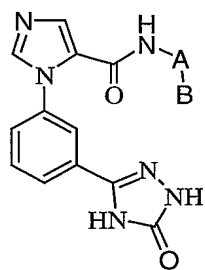
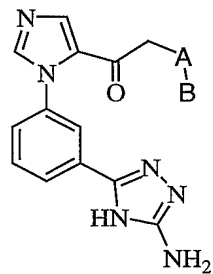
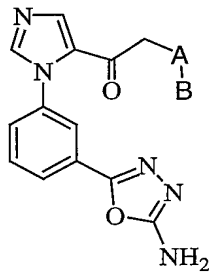
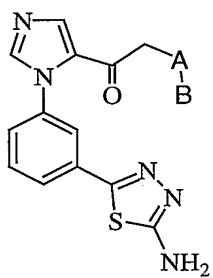
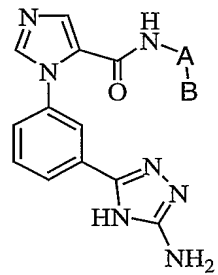
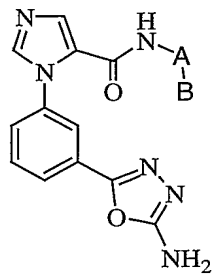
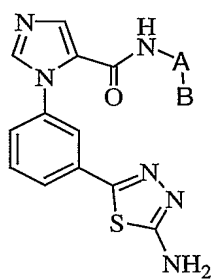
Examples -360 use the structures from Table 1 and the corresponding A and B groups from Examples -360 of Table 1, and:

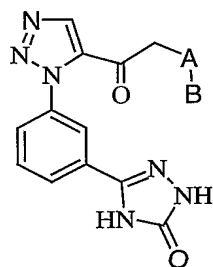
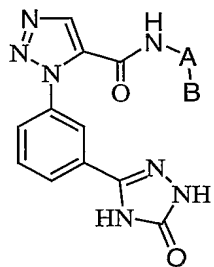
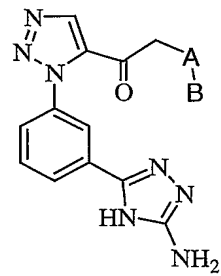
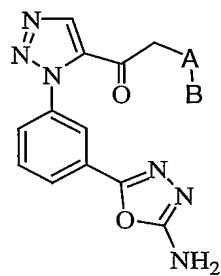
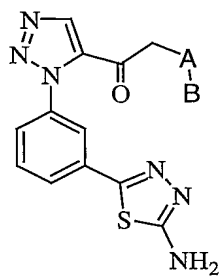
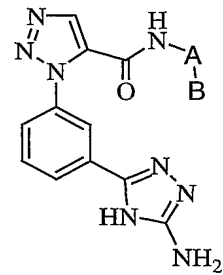
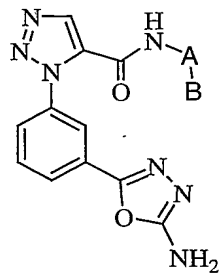
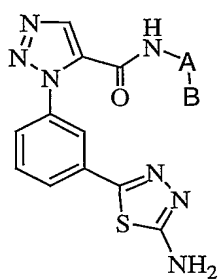
R^{1a} is 1-tetrazolyl-CH₂-.

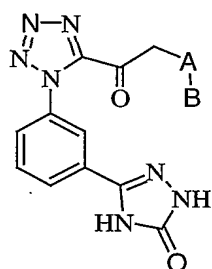
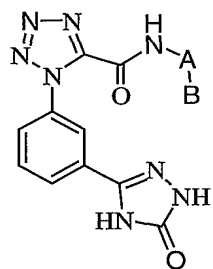
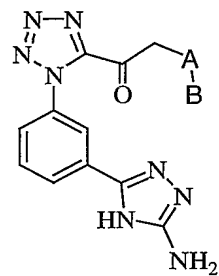
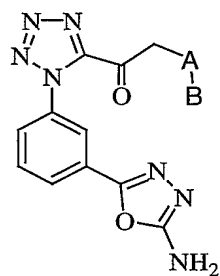
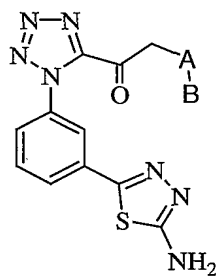
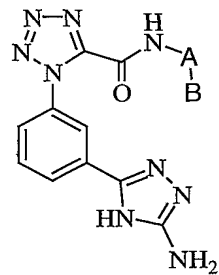
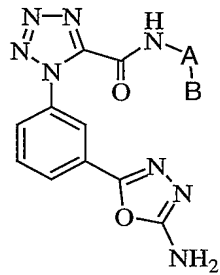
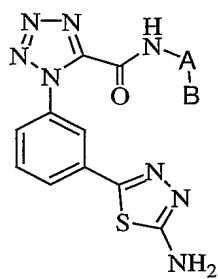
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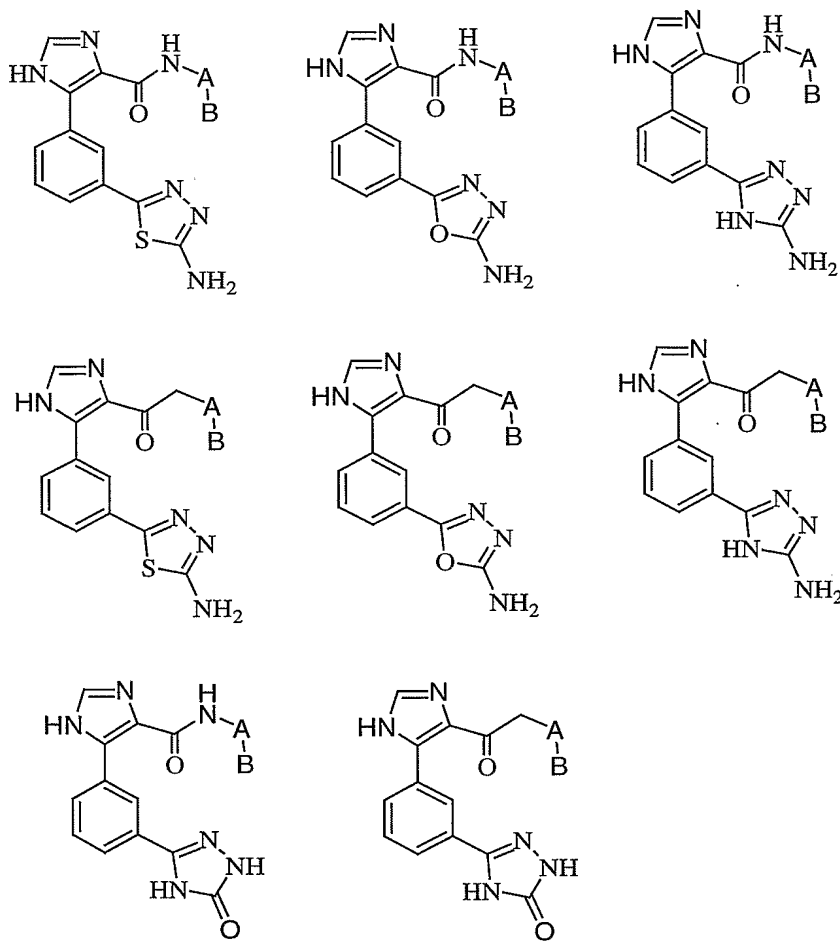
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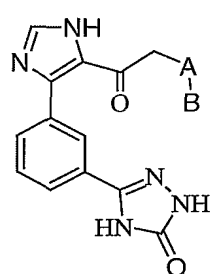
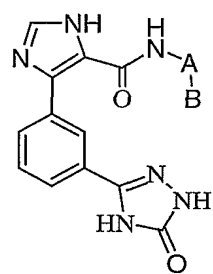
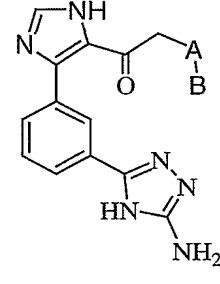
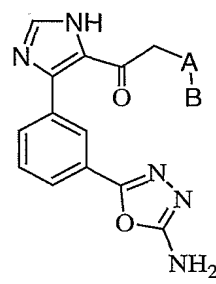
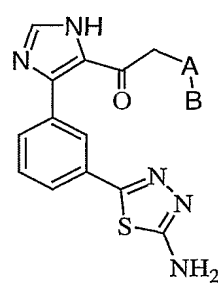
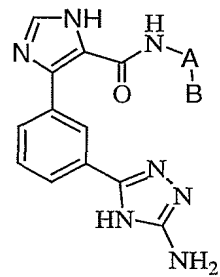
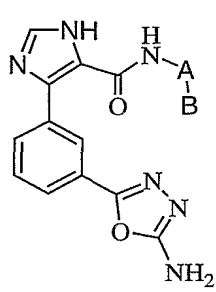
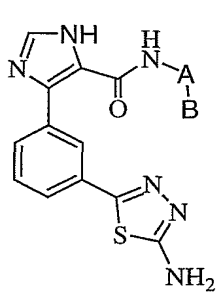


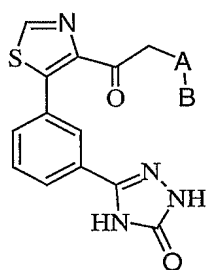
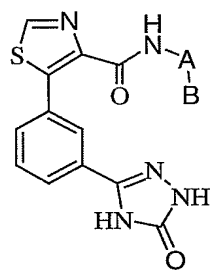
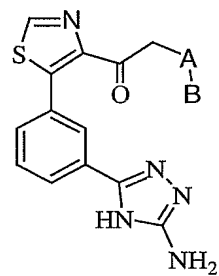
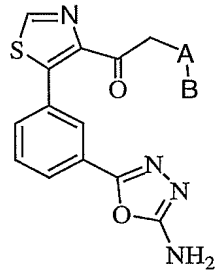
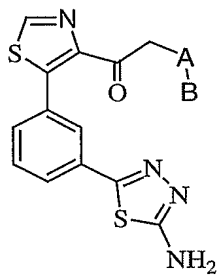
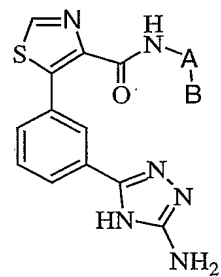
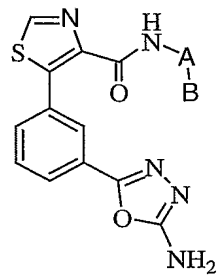
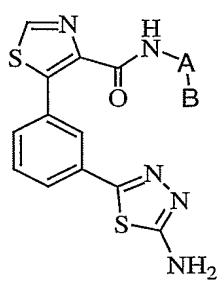


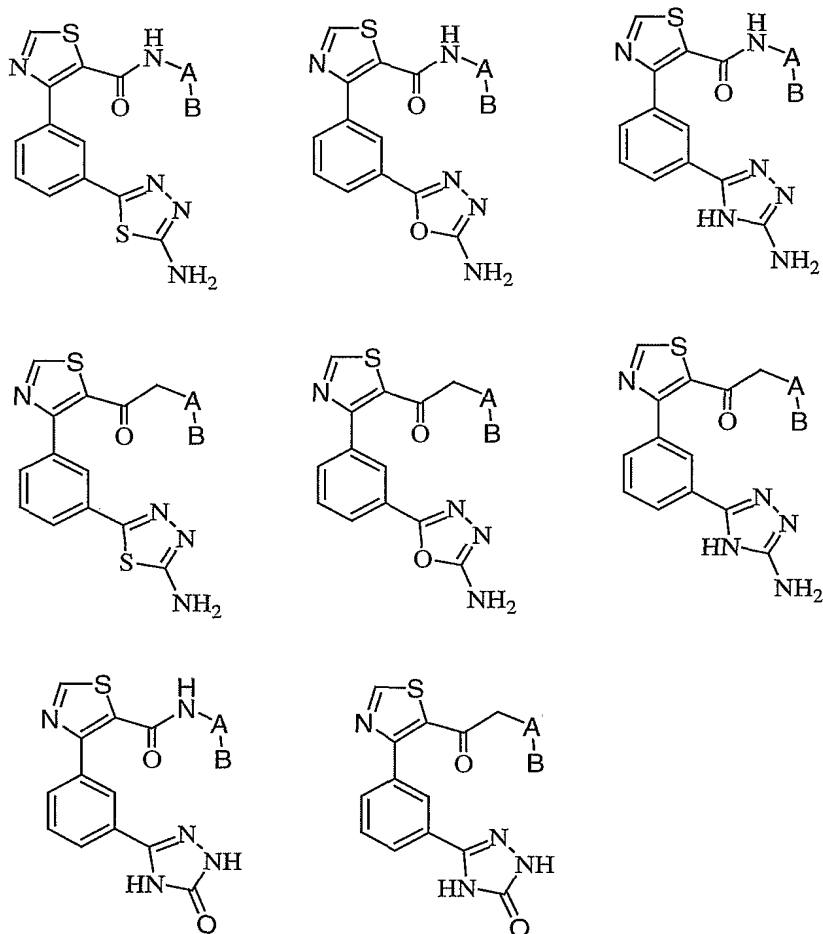












Ex#	A	B
5	1. phenyl	2-(NH ₂ SO ₂)phenyl
	2. phenyl	2-(CH ₃ SO ₂)phenyl
	3. phenyl	3-NH ₂ SO ₂ -4-pyridyl
	4. phenyl	3-CH ₃ SO ₂ -4-pyridyl
	5. phenyl	2-(CH ₃ NH)phenyl
	6. phenyl	3-((CH ₃) ₂ NCH ₂)-4-pyridyl
10	7. phenyl	2-(N-(3-R-HO-pyrrolidinyl)CH ₂)phenyl
	8. phenyl	2-(N-(4-HO-piperidinyl)CH ₂)phenyl
	9. phenyl	2-((CH ₃) ₂ NCH ₂)phenyl
15	10. phenyl	2-((CH ₃)NHCH ₂)phenyl
	11. phenyl	2-((CH ₃ CH ₂)NHCH ₂)phenyl
	12. phenyl	2-((CH ₃ CH ₂) ₂ NCH ₂)phenyl
	13. phenyl	2-((CH ₃ CH ₂)N(CH ₃)CH ₂)phenyl
	14. phenyl	2-(((CH ₃) ₂ CH)NHCH ₂)phenyl
	15. phenyl	2-(((CH ₃) ₂ CH) ₂ NCH ₂)phenyl
20	16. phenyl	2-((cyclopropyl)NHCH ₂)phenyl
	17. phenyl	2-((cyclopropyl) ₂ NCH ₂)phenyl
	18. phenyl	2-((cyclobutyl)NHCH ₂)phenyl
	19. phenyl	2-((cyclobutyl) ₂ NCH ₂)phenyl
	20. phenyl	2-((cyclopentyl)NHCH ₂)phenyl
	21. phenyl	2-((cyclopentyl) ₂ NCH ₂)phenyl

	22.	phenyl	2-((cyclohexyl)NHCH ₂)phenyl
	23.	phenyl	2-((cyclohexyl) ₂ NCH ₂)phenyl
	24.	phenyl	1-CH ₃ -2-imidazolyl
	25.	phenyl	2-CH ₃ -1-imidazolyl
5	26.	phenyl	2-((CH ₃) ₂ NCH ₂)-1-imidazolyl
	27.	phenyl	2-((CH ₃)NHCH ₂)-1-imidazolyl
	28.	phenyl	2-((CH ₃ CH ₂)NHCH ₂)-1-imidazolyl
	29.	phenyl	2-((CH ₃ CH ₂) ₂ NCH ₂)-1-imidazolyl
	30.	phenyl	2-((CH ₃ CH ₂)N(CH ₃)CH ₂)-1-imidazolyl
10	31.	phenyl	2-(((CH ₃) ₂ CH)NHCH ₂)-1-imidazolyl
	32.	phenyl	2-(((CH ₃) ₂ CH) ₂ NCH ₂)-1-imidazolyl
	33.	phenyl	2-((cyclopropyl)NHCH ₂)-1-imidazolyl
	34.	phenyl	2-((cyclopropyl) ₂ NCH ₂)-1-imidazolyl
	35.	phenyl	2-((cyclobutyl)NHCH ₂)-1-imidazolyl
15	36.	phenyl	2-((cyclobutyl) ₂ NCH ₂)-1-imidazolyl
	37.	phenyl	2-((cyclopentyl)NHCH ₂)-1-imidazolyl
	38.	phenyl	2-((cyclopentyl) ₂ NCH ₂)-1-imidazolyl
	39.	phenyl	2-((cyclohexyl)NHCH ₂)-1-imidazolyl
	40.	phenyl	2-((cyclohexyl) ₂ NCH ₂)-1-imidazolyl
20	41.	2-pyridyl	2-(NH ₂ SO ₂)phenyl
	42.	2-pyridyl	2-(CH ₃ SO ₂)phenyl
	43.	2-pyridyl	3-NH ₂ SO ₂ -4-pyridyl
	44.	2-pyridyl	3-CH ₃ SO ₂ -4-pyridyl
	45.	2-pyridyl	2-(CH ₃ NH)phenyl
25	46.	2-pyridyl	3-((CH ₃) ₂ NCH ₂)-4-pyridyl
	47.	2-pyridyl	2-(N-(3-R-HO-pyrrolidinyl)CH ₂)phenyl
	48.	2-pyridyl	2-(N-(4-HO-piperidinyl)CH ₂)phenyl
	49.	2-pyridyl	2-((CH ₃) ₂ NCH ₂)phenyl
	50.	2-pyridyl	2-((CH ₃)NHCH ₂)phenyl
30	51.	2-pyridyl	2-((CH ₃ CH ₂)NHCH ₂)phenyl
	52.	2-pyridyl	2-((CH ₃ CH ₂) ₂ NCH ₂)phenyl
	53.	2-pyridyl	2-((CH ₃ CH ₂)N(CH ₃)CH ₂)phenyl
	54.	2-pyridyl	2-(((CH ₃) ₂ CH)NHCH ₂)phenyl
	55.	2-pyridyl	2-(((CH ₃) ₂ CH) ₂ NCH ₂)phenyl
35	56.	2-pyridyl	2-((cyclopropyl)NHCH ₂)phenyl
	57.	2-pyridyl	2-((cyclopropyl) ₂ NCH ₂)phenyl
	58.	2-pyridyl	2-((cyclobutyl)NHCH ₂)phenyl
	59.	2-pyridyl	2-((cyclobutyl) ₂ NCH ₂)phenyl
	60.	2-pyridyl	2-((cyclopentyl)NHCH ₂)phenyl
40	61.	2-pyridyl	2-((cyclopentyl) ₂ NCH ₂)phenyl
	62.	2-pyridyl	2-((cyclohexyl)NHCH ₂)phenyl
	63.	2-pyridyl	2-((cyclohexyl) ₂ NCH ₂)phenyl
	64.	2-pyridyl	1-CH ₃ -2-imidazolyl
	65.	2-pyridyl	2-CH ₃ -1-imidazolyl
45	66.	2-pyridyl	2-((CH ₃) ₂ NCH ₂)-1-imidazolyl
	67.	2-pyridyl	2-((CH ₃)NHCH ₂)-1-imidazolyl
	68.	2-pyridyl	2-((CH ₃ CH ₂)NHCH ₂)-1-imidazolyl
	69.	2-pyridyl	2-((CH ₃ CH ₂) ₂ NCH ₂)-1-imidazolyl
	70.	2-pyridyl	2-((CH ₃ CH ₂)N(CH ₃)CH ₂)-1-imidazolyl
50	71.	2-pyridyl	2-(((CH ₃) ₂ CH)NHCH ₂)-1-imidazolyl
	72.	2-pyridyl	2-(((CH ₃) ₂ CH) ₂ NCH ₂)-1-imidazolyl
	73.	2-pyridyl	2-((cyclopropyl)NHCH ₂)-1-imidazolyl
	74.	2-pyridyl	2-((cyclopropyl) ₂ NCH ₂)-1-imidazolyl

	75.	2-pyridyl	2-((cyclobutyl)NHCH ₂)-1-imidazolyl
	76.	2-pyridyl	2-((cyclobutyl) ₂ NCH ₂)-1-imidazolyl
	77.	2-pyridyl	2-((cyclopentyl)NHCH ₂)-1-imidazolyl
	78.	2-pyridyl	2-((cyclopentyl) ₂ NCH ₂)-1-imidazolyl
5	79.	2-pyridyl	2-((cyclohexyl)NHCH ₂)-1-imidazolyl
	80.	2-pyridyl	2-((cyclohexyl) ₂ NCH ₂)-1-imidazolyl
	81.	3-pyridyl	2-(NH ₂ SO ₂)phenyl
	82.	3-pyridyl	2-(CH ₃ SO ₂)phenyl
	83.	3-pyridyl	3-NH ₂ SO ₂ -4-pyridyl
10	84.	3-pyridyl	3-CH ₃ SO ₂ -4-pyridyl
	85.	3-pyridyl	2-(CH ₃ NH)phenyl
	86.	3-pyridyl	3-((CH ₃) ₂ NCH ₂)-4-pyridyl
	87.	3-pyridyl	2-(N-(3-R-HO-pyrrolidinyl)CH ₂)phenyl
	88.	3-pyridyl	2-(N-(4-HO-piperidinyl)CH ₂)phenyl
15	89.	3-pyridyl	2-((CH ₃) ₂ NCH ₂)phenyl
	90.	3-pyridyl	2-((CH ₃)NHCH ₂)phenyl
	91.	3-pyridyl	2-((CH ₃ CH ₂)NHCH ₂)phenyl
	92.	3-pyridyl	2-((CH ₃ CH ₂) ₂ NCH ₂)phenyl
	93.	3-pyridyl	2-((CH ₃ CH ₂)N(CH ₃)CH ₂)phenyl
20	94.	3-pyridyl	2-(((CH ₃) ₂ CH)NHCH ₂)phenyl
	95.	3-pyridyl	2-(((CH ₃) ₂ CH) ₂ NCH ₂)phenyl
	96.	3-pyridyl	2-((cyclopropyl)NHCH ₂)phenyl
	97.	3-pyridyl	2-((cyclopropyl) ₂ NCH ₂)phenyl
	98.	3-pyridyl	2-((cyclobutyl)NHCH ₂)phenyl
25	99.	3-pyridyl	2-((cyclobutyl) ₂ NCH ₂)phenyl
	100.	3-pyridyl	2-((cyclopentyl)NHCH ₂)phenyl
	101.	3-pyridyl	2-((cyclopentyl) ₂ NCH ₂)phenyl
	102.	3-pyridyl	2-((cyclohexyl)NHCH ₂)phenyl
	103.	3-pyridyl	2-((cyclohexyl) ₂ NCH ₂)phenyl
30	104.	3-pyridyl	1-CH ₃ -2-imidazolyl
	105.	3-pyridyl	2-CH ₃ -1-imidazolyl
	106.	3-pyridyl	2-((CH ₃) ₂ NCH ₂)-1-imidazolyl
	107.	3-pyridyl	2-((CH ₃)NHCH ₂)-1-imidazolyl
	108.	3-pyridyl	2-((CH ₃ CH ₂)NHCH ₂)-1-imidazolyl
35	109.	3-pyridyl	2-((CH ₃ CH ₂) ₂ NCH ₂)-1-imidazolyl
	110.	3-pyridyl	2-((CH ₃ CH ₂)N(CH ₃)CH ₂)-1-imidazolyl
	111.	3-pyridyl	2-(((CH ₃) ₂ CH)NHCH ₂)-1-imidazolyl
	112.	3-pyridyl	2-(((CH ₃) ₂ CH) ₂ NCH ₂)-1-imidazolyl
	113.	3-pyridyl	2-((cyclopropyl)NHCH ₂)-1-imidazolyl
40	114.	3-pyridyl	2-((cyclopropyl) ₂ NCH ₂)-1-imidazolyl
	115.	3-pyridyl	2-((cyclobutyl)NHCH ₂)-1-imidazolyl
	116.	3-pyridyl	2-((cyclobutyl) ₂ NCH ₂)-1-imidazolyl
	117.	3-pyridyl	2-((cyclopentyl)NHCH ₂)-1-imidazolyl
	118.	3-pyridyl	2-((cyclopentyl) ₂ NCH ₂)-1-imidazolyl
45	119.	3-pyridyl	2-((cyclohexyl)NHCH ₂)-1-imidazolyl
	120.	3-pyridyl	2-((cyclohexyl) ₂ NCH ₂)-1-imidazolyl
	121.	2-pyrimidyl	2-(NH ₂ SO ₂)phenyl
	122.	2-pyrimidyl	2-(CH ₃ SO ₂)phenyl
	123.	2-pyrimidyl	3-NH ₂ SO ₂ -4-pyridyl
50	124.	2-pyrimidyl	3-CH ₃ SO ₂ -4-pyridyl
	125.	2-pyrimidyl	2-(CH ₃ NH)phenyl
	126.	2-pyrimidyl	3-((CH ₃) ₂ NCH ₂)-4-pyridyl
	127.	2-pyrimidyl	2-(N-(3-R-HO-pyrrolidinyl)CH ₂)phenyl

	128.	2-pyrimidyl	2-(N-(4-HO-piperidinyl)CH ₂)phenyl
	129.	2-pyrimidyl	2-((CH ₃) ₂ NCH ₂)phenyl
	130.	2-pyrimidyl	2-((CH ₃)NHCH ₂)phenyl
	131.	2-pyrimidyl	2-((CH ₃ CH ₂)NHCH ₂)phenyl
5	132.	2-pyrimidyl	2-((CH ₃ CH ₂) ₂ NCH ₂)phenyl
	133.	2-pyrimidyl	2-((CH ₃ CH ₂)N(CH ₃)CH ₂)phenyl
	134.	2-pyrimidyl	2-(((CH ₃) ₂ CH)NHCH ₂)phenyl
	135.	2-pyrimidyl	2-(((CH ₃) ₂ CH) ₂ NCH ₂)phenyl
	136.	2-pyrimidyl	2-((cyclopropyl)NHCH ₂)phenyl
10	137.	2-pyrimidyl	2-((cyclopropyl) ₂ NCH ₂)phenyl
	138.	2-pyrimidyl	2-((cyclobutyl)NHCH ₂)phenyl
	139.	2-pyrimidyl	2-((cyclobutyl) ₂ NCH ₂)phenyl
	140.	2-pyrimidyl	2-((cyclopentyl)NHCH ₂)phenyl
	141.	2-pyrimidyl	2-((cyclopentyl) ₂ NCH ₂)phenyl
15	142.	2-pyrimidyl	2-((cyclohexyl)NHCH ₂)phenyl
	143.	2-pyrimidyl	2-((cyclohexyl) ₂ NCH ₂)phenyl
	144.	2-pyrimidyl	1-CH ₃ -2-imidazolyl
	145.	2-pyrimidyl	2-CH ₃ -1-imidazolyl
	146.	2-pyrimidyl	2-((CH ₃) ₂ NCH ₂)-1-imidazolyl
20	147.	2-pyrimidyl	2-((CH ₃)NHCH ₂)-1-imidazolyl
	148.	2-pyrimidyl	2-((CH ₃ CH ₂)NHCH ₂)-1-imidazolyl
	149.	2-pyrimidyl	2-((CH ₃ CH ₂) ₂ NCH ₂)-1-imidazolyl
	150.	2-pyrimidyl	2-((CH ₃ CH ₂)N(CH ₃)CH ₂)-1-imidazolyl
	151.	2-pyrimidyl	2-(((CH ₃) ₂ CH)NHCH ₂)-1-imidazolyl
25	152.	2-pyrimidyl	2-(((CH ₃) ₂ CH) ₂ NCH ₂)-1-imidazolyl
	153.	2-pyrimidyl	2-((cyclopropyl)NHCH ₂)-1-imidazolyl
	154.	2-pyrimidyl	2-((cyclopropyl) ₂ NCH ₂)-1-imidazolyl
	155.	2-pyrimidyl	2-((cyclobutyl)NHCH ₂)-1-imidazolyl
	156.	2-pyrimidyl	2-((cyclobutyl) ₂ NCH ₂)-1-imidazolyl
30	157.	2-pyrimidyl	2-((cyclopentyl)NHCH ₂)-1-imidazolyl
	158.	2-pyrimidyl	2-((cyclopentyl) ₂ NCH ₂)-1-imidazolyl
	159.	2-pyrimidyl	2-((cyclohexyl)NHCH ₂)-1-imidazolyl
	160.	2-pyrimidyl	2-((cyclohexyl) ₂ NCH ₂)-1-imidazolyl
	161.	5-pyrimidyl	2-(NH ₂ SO ₂)phenyl
35	162.	5-pyrimidyl	2-(CH ₃ SO ₂)phenyl
	163.	5-pyrimidyl	3-NH ₂ SO ₂ -4-pyridyl
	164.	5-pyrimidyl	3-CH ₃ SO ₂ -4-pyridyl
	165.	5-pyrimidyl	2-(CH ₃ NH)phenyl
	166.	5-pyrimidyl	3-((CH ₃) ₂ NCH ₂)-4-pyridyl
40	167.	5-pyrimidyl	2-(N-(3-R-HO-pyrrolidinyl)CH ₂)phenyl
	168.	5-pyrimidyl	2-(N-(4-HO-piperidinyl)CH ₂)phenyl
	169.	5-pyrimidyl	2-((CH ₃) ₂ NCH ₂)phenyl
	170.	5-pyrimidyl	2-((CH ₃)NHCH ₂)phenyl
	171.	5-pyrimidyl	2-((CH ₃ CH ₂)NHCH ₂)phenyl
45	172.	5-pyrimidyl	2-((CH ₃ CH ₂) ₂ NCH ₂)phenyl
	173.	5-pyrimidyl	2-((CH ₃ CH ₂)N(CH ₃)CH ₂)phenyl
	174.	5-pyrimidyl	2-(((CH ₃) ₂ CH)NHCH ₂)phenyl
	175.	5-pyrimidyl	2-(((CH ₃) ₂ CH) ₂ NCH ₂)phenyl
	176.	5-pyrimidyl	2-((cyclopropyl)NHCH ₂)phenyl
50	177.	5-pyrimidyl	2-((cyclopropyl) ₂ NCH ₂)phenyl
	178.	5-pyrimidyl	2-((cyclobutyl)NHCH ₂)phenyl
	179.	5-pyrimidyl	2-((cyclobutyl) ₂ NCH ₂)phenyl
	180.	5-pyrimidyl	2-((cyclopentyl)NHCH ₂)phenyl

	181.	5-pyrimidyl	2-((cyclopentyl) ₂ NCH ₂)phenyl
	182.	5-pyrimidyl	2-((cyclohexyl)NHCH ₂)phenyl
	183.	5-pyrimidyl	2-((cyclohexyl) ₂ NCH ₂)phenyl
	184.	5-pyrimidyl	1-CH ₃ -2-imidazolyl
5	185.	5-pyrimidyl	2-CH ₃ -1-imidazolyl
	186.	5-pyrimidyl	2-((CH ₃) ₂ NCH ₂)-1-imidazolyl
	187.	5-pyrimidyl	2-((CH ₃)NHCH ₂)-1-imidazolyl
	188.	5-pyrimidyl	2-((CH ₃ CH ₂)NHCH ₂)-1-imidazolyl
	189.	5-pyrimidyl	2-((CH ₃ CH ₂) ₂ NCH ₂)-1-imidazolyl
10	190.	5-pyrimidyl	2-((CH ₃ CH ₂)N(CH ₃)CH ₂)-1-imidazolyl
	191.	5-pyrimidyl	2-(((CH ₃) ₂ CH)NHCH ₂)-1-imidazolyl
	192.	5-pyrimidyl	2-(((CH ₃) ₂ CH) ₂ NCH ₂)-1-imidazolyl
	193.	5-pyrimidyl	2-((cyclopropyl)NHCH ₂)-1-imidazolyl
	194.	5-pyrimidyl	2-((cyclopropyl) ₂ NCH ₂)-1-imidazolyl
15	195.	5-pyrimidyl	2-((cyclobutyl)NHCH ₂)-1-imidazolyl
	196.	5-pyrimidyl	2-((cyclobutyl) ₂ NCH ₂)-1-imidazolyl
	197.	5-pyrimidyl	2-((cyclopentyl)NHCH ₂)-1-imidazolyl
	198.	5-pyrimidyl	2-((cyclopentyl) ₂ NCH ₂)-1-imidazolyl
	199.	5-pyrimidyl	2-((cyclohexyl)NHCH ₂)-1-imidazolyl
20	200.	5-pyrimidyl	2-((cyclohexyl) ₂ NCH ₂)-1-imidazolyl
	201.	2-Cl-phenyl	2-(NH ₂ SO ₂)phenyl
	202.	2-Cl-phenyl	2-(CH ₃ SO ₂)phenyl
	203.	2-Cl-phenyl	3-NH ₂ SO ₂ -4-pyridyl
	204.	2-Cl-phenyl	3-CH ₃ SO ₂ -4-pyridyl
25	205.	2-Cl-phenyl	2-(CH ₃ NH)phenyl
	206.	2-Cl-phenyl	3-((CH ₃) ₂ NCH ₂)-4-pyridyl
	207.	2-Cl-phenyl	2-(N-(3-R-HO-pyrrolidinyl)CH ₂)phenyl
	208.	2-Cl-phenyl	2-(N-(4-HO-piperidinyl)CH ₂)phenyl
	209.	2-Cl-phenyl	2-((CH ₃) ₂ NCH ₂)phenyl
30	210.	2-Cl-phenyl	2-((CH ₃)NHCH ₂)phenyl
	211.	2-Cl-phenyl	2-((CH ₃ CH ₂)NHCH ₂)phenyl
	212.	2-Cl-phenyl	2-((CH ₃ CH ₂) ₂ NCH ₂)phenyl
	213.	2-Cl-phenyl	2-((CH ₃ CH ₂)N(CH ₃)CH ₂)phenyl
	214.	2-Cl-phenyl	2-(((CH ₃) ₂ CH)NHCH ₂)phenyl
35	215.	2-Cl-phenyl	2-(((CH ₃) ₂ CH) ₂ NCH ₂)phenyl
	216.	2-Cl-phenyl	2-((cyclopropyl)NHCH ₂)phenyl
	217.	2-Cl-phenyl	2-((cyclopropyl) ₂ NCH ₂)phenyl
	218.	2-Cl-phenyl	2-((cyclobutyl)NHCH ₂)phenyl
	219.	2-Cl-phenyl	2-((cyclobutyl) ₂ NCH ₂)phenyl
40	220.	2-Cl-phenyl	2-((cyclopentyl)NHCH ₂)phenyl
	221.	2-Cl-phenyl	2-((cyclopentyl) ₂ NCH ₂)phenyl
	222.	2-Cl-phenyl	2-((cyclohexyl)NHCH ₂)phenyl
	223.	2-Cl-phenyl	2-((cyclohexyl) ₂ NCH ₂)phenyl
	224.	2-Cl-phenyl	1-CH ₃ -2-imidazolyl
45	225.	2-Cl-phenyl	2-CH ₃ -1-imidazolyl
	226.	2-Cl-phenyl	2-((CH ₃) ₂ NCH ₂)-1-imidazolyl
	227.	2-Cl-phenyl	2-((CH ₃)NHCH ₂)-1-imidazolyl
	228.	2-Cl-phenyl	2-((CH ₃ CH ₂)NHCH ₂)-1-imidazolyl
	229.	2-Cl-phenyl	2-((CH ₃ CH ₂) ₂ NCH ₂)-1-imidazolyl
50	230.	2-Cl-phenyl	2-((CH ₃ CH ₂)N(CH ₃)CH ₂)-1-imidazolyl
	231.	2-Cl-phenyl	2-(((CH ₃) ₂ CH)NHCH ₂)-1-imidazolyl
	232.	2-Cl-phenyl	2-(((CH ₃) ₂ CH) ₂ NCH ₂)-1-imidazolyl
	233.	2-Cl-phenyl	2-((cyclopropyl)NHCH ₂)-1-imidazolyl

	234.	2-Cl-phenyl	2-((cyclopropyl) ₂ NCH ₂)-1-imidazolyl
	235.	2-Cl-phenyl	2-((cyclobutyl)NHCH ₂)-1-imidazolyl
	236.	2-Cl-phenyl	2-((cyclobutyl) ₂ NCH ₂)-1-imidazolyl
5	237.	2-Cl-phenyl	2-((cyclopentyl)NHCH ₂)-1-imidazolyl
	238.	2-Cl-phenyl	2-((cyclopentyl) ₂ NCH ₂)-1-imidazolyl
	239.	2-Cl-phenyl	2-((cyclohexyl)NHCH ₂)-1-imidazolyl
	240.	2-Cl-phenyl	2-((cyclohexyl) ₂ NCH ₂)-1-imidazolyl
	241.	2-F-phenyl	2-(NH ₂ SO ₂)phenyl
	242.	2-F-phenyl	2-(CH ₃ SO ₂)phenyl
10	243.	2-F-phenyl	3-NH ₂ SO ₂ -4-pyridyl
	244.	2-F-phenyl	3-CH ₃ SO ₂ -4-pyridyl
	245.	2-F-phenyl	2-(CH ₃ NH)phenyl
	246.	2-F-phenyl	3-((CH ₃) ₂ NCH ₂)-4-pyridyl
15	247.	2-F-phenyl	2-(N-(3-R-HO-pyrrolidinyl)CH ₂)phenyl
	248.	2-F-phenyl	2-(N-(4-HO-piperidinyl)CH ₂)phenyl
	249.	2-F-phenyl	2-((CH ₃) ₂ NCH ₂)phenyl
	250.	2-F-phenyl	2-((CH ₃)NHCH ₂)phenyl
	251.	2-F-phenyl	2-((CH ₃ CH ₂)NHCH ₂)phenyl
	252.	2-F-phenyl	2-((CH ₃ CH ₂) ₂ NCH ₂)phenyl
20	253.	2-F-phenyl	2-((CH ₃ CH ₂)N(CH ₃)CH ₂)phenyl
	254.	2-F-phenyl	2-(((CH ₃) ₂ CH)NHCH ₂)phenyl
	255.	2-F-phenyl	2-(((CH ₃) ₂ CH) ₂ NCH ₂)phenyl
	256.	2-F-phenyl	2-((cyclopropyl)NHCH ₂)phenyl
	257.	2-F-phenyl	2-((cyclopropyl) ₂ NCH ₂)phenyl
25	258.	2-F-phenyl	2-((cyclobutyl)NHCH ₂)phenyl
	259.	2-F-phenyl	2-((cyclobutyl) ₂ NCH ₂)phenyl
	260.	2-F-phenyl	2-((cyclopentyl)NHCH ₂)phenyl
	261.	2-F-phenyl	2-((cyclopentyl) ₂ NCH ₂)phenyl
	262.	2-F-phenyl	2-((cyclohexyl)NHCH ₂)phenyl
30	263.	2-F-phenyl	2-((cyclohexyl) ₂ NCH ₂)phenyl
	264.	2-F-phenyl	1-CH ₃ -2-imidazolyl
	265.	2-F-phenyl	2-CH ₃ -1-imidazolyl
	266.	2-F-phenyl	2-((CH ₃) ₂ NCH ₂)-1-imidazolyl
	267.	2-F-phenyl	2-((CH ₃)NHCH ₂)-1-imidazolyl
35	268.	2-F-phenyl	2-((CH ₃ CH ₂)NHCH ₂)-1-imidazolyl
	269.	2-F-phenyl	2-((CH ₃ CH ₂) ₂ NCH ₂)-1-imidazolyl
	270.	2-F-phenyl	2-((CH ₃ CH ₂)N(CH ₃)CH ₂)-1-imidazolyl
	271.	2-F-phenyl	2-(((CH ₃) ₂ CH)NHCH ₂)-1-imidazolyl
	272.	2-F-phenyl	2-(((CH ₃) ₂ CH) ₂ NCH ₂)-1-imidazolyl
40	273.	2-F-phenyl	2-((cyclopropyl)NHCH ₂)-1-imidazolyl
	274.	2-F-phenyl	2-((cyclopropyl) ₂ NCH ₂)-1-imidazolyl
	275.	2-F-phenyl	2-((cyclobutyl)NHCH ₂)-1-imidazolyl
	276.	2-F-phenyl	2-((cyclobutyl) ₂ NCH ₂)-1-imidazolyl
	277.	2-F-phenyl	2-((cyclopentyl)NHCH ₂)-1-imidazolyl
45	278.	2-F-phenyl	2-((cyclopentyl) ₂ NCH ₂)-1-imidazolyl
	279.	2-F-phenyl	2-((cyclohexyl)NHCH ₂)-1-imidazolyl
	280.	2-F-phenyl	2-((cyclohexyl) ₂ NCH ₂)-1-imidazolyl
	281.	2,6-diF-phenyl	2-(NH ₂ SO ₂)phenyl
	282.	2,6-diF-phenyl	2-(CH ₃ SO ₂)phenyl
50	283.	2,6-diF-phenyl	3-NH ₂ SO ₂ -4-pyridyl
	284.	2,6-diF-phenyl	3-CH ₃ SO ₂ -4-pyridyl
	285.	2,6-diF-phenyl	2-(CH ₃ NH)phenyl
	286.	2,6-diF-phenyl	3-((CH ₃) ₂ NCH ₂)-4-pyridyl

	287.	2,6-diF-phenyl	2-(N-(3-R-HO-pyrrolidinyl)CH ₂)phenyl
	288.	2,6-diF-phenyl	2-(N-(4-HO-piperidinyl)CH ₂)phenyl
	289.	2,6-diF-phenyl	2-((CH ₃) ₂ NCH ₂)phenyl
	290.	2,6-diF-phenyl	2-((CH ₃)NHCH ₂)phenyl
5	291.	2,6-diF-phenyl	2-((CH ₃ CH ₂)NHCH ₂)phenyl
	292.	2,6-diF-phenyl	2-((CH ₃ CH ₂) ₂ NCH ₂)phenyl
	293.	2,6-diF-phenyl	2-((CH ₃ CH ₂)N(CH ₃)CH ₂)phenyl
	294.	2,6-diF-phenyl	2-(((CH ₃) ₂ CH)NHCH ₂)phenyl
	295.	2,6-diF-phenyl	2-(((CH ₃) ₂ CH) ₂ NCH ₂)phenyl
10	296.	2,6-diF-phenyl	2-((cyclopropyl)NHCH ₂)phenyl
	297.	2,6-diF-phenyl	2-((cyclopropyl) ₂ NCH ₂)phenyl
	298.	2,6-diF-phenyl	2-((cyclobutyl)NHCH ₂)phenyl
	299.	2,6-diF-phenyl	2-((cyclobutyl) ₂ NCH ₂)phenyl
	300.	2,6-diF-phenyl	2-((cyclopentyl)NHCH ₂)phenyl
15	301.	2,6-diF-phenyl	2-((cyclopentyl) ₂ NCH ₂)phenyl
	302.	2,6-diF-phenyl	2-((cyclohexyl)NHCH ₂)phenyl
	303.	2,6-diF-phenyl	2-((cyclohexyl) ₂ NCH ₂)phenyl
	304.	2,6-diF-phenyl	1-CH ₃ -2-imidazolyl
	305.	2,6-diF-phenyl	2-CH ₃ -1-imidazolyl
20	306.	2,6-diF-phenyl	2-((CH ₃) ₂ NCH ₂)-1-imidazolyl
	307.	2,6-diF-phenyl	2-((CH ₃)NHCH ₂)-1-imidazolyl
	308.	2,6-diF-phenyl	2-((CH ₃ CH ₂)NHCH ₂)-1-imidazolyl
	309.	2,6-diF-phenyl	2-((CH ₃ CH ₂) ₂ NCH ₂)-1-imidazolyl
	310.	2,6-diF-phenyl	2-((CH ₃ CH ₂)N(CH ₃)CH ₂)-1-imidazolyl
25	311.	2,6-diF-phenyl	2-(((CH ₃) ₂ CH)NHCH ₂)-1-imidazolyl
	312.	2,6-diF-phenyl	2-(((CH ₃) ₂ CH) ₂ NCH ₂)-1-imidazolyl
	313.	2,6-diF-phenyl	2-((cyclopropyl)NHCH ₂)-1-imidazolyl
	314.	2,6-diF-phenyl	2-((cyclopropyl) ₂ NCH ₂)-1-imidazolyl
	315.	2,6-diF-phenyl	2-((cyclobutyl)NHCH ₂)-1-imidazolyl
30	316.	2,6-diF-phenyl	2-((cyclobutyl) ₂ NCH ₂)-1-imidazolyl
	317.	2,6-diF-phenyl	2-((cyclopentyl)NHCH ₂)-1-imidazolyl
	318.	2,6-diF-phenyl	2-((cyclopentyl) ₂ NCH ₂)-1-imidazolyl
	319.	2,6-diF-phenyl	2-((cyclohexyl)NHCH ₂)-1-imidazolyl
	320.	2,6-diF-phenyl	2-((cyclohexyl) ₂ NCH ₂)-1-imidazolyl
35	321.	piperidinyl	2-(NH ₂ SO ₂)phenyl
	322.	piperidinyl	2-(CH ₃ SO ₂)phenyl
	323.	piperidinyl	3-NH ₂ SO ₂ -4-pyridyl
	324.	piperidinyl	3-CH ₃ SO ₂ -4-pyridyl
	325.	piperidinyl	2-(CH ₃ NH)phenyl
40	326.	piperidinyl	3-((CH ₃) ₂ NCH ₂)-4-pyridyl
	327.	piperidinyl	2-(N-(3-R-HO-pyrrolidinyl)CH ₂)phenyl
	328.	piperidinyl	2-(N-(4-HO-piperidinyl)CH ₂)phenyl
	329.	piperidinyl	2-((CH ₃) ₂ NCH ₂)phenyl
	330.	piperidinyl	2-((CH ₃)NHCH ₂)phenyl
45	331.	piperidinyl	2-((CH ₃ CH ₂)NHCH ₂)phenyl
	332.	piperidinyl	2-((CH ₃ CH ₂) ₂ NCH ₂)phenyl
	333.	piperidinyl	2-((CH ₃ CH ₂)N(CH ₃)CH ₂)phenyl
	334.	piperidinyl	2-(((CH ₃) ₂ CH)NHCH ₂)phenyl
	335.	piperidinyl	2-(((CH ₃) ₂ CH) ₂ NCH ₂)phenyl
50	336.	piperidinyl	2-((cyclopropyl)NHCH ₂)phenyl
	337.	piperidinyl	2-((cyclopropyl) ₂ NCH ₂)phenyl
	338.	piperidinyl	2-((cyclobutyl)NHCH ₂)phenyl
	339.	piperidinyl	2-((cyclobutyl) ₂ NCH ₂)phenyl

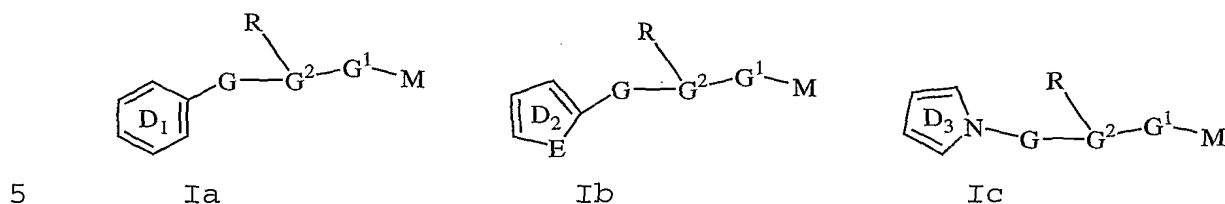
340. piperidiny1 2-((cyclopentyl)NHCH₂)phenyl
341. piperidiny1 2-((cyclopentyl)₂NCH₂)phenyl
342. piperidiny1 2-((cyclohexyl)NHCH₂)phenyl
343. piperidiny1 2-((cyclohexyl)₂NCH₂)phenyl
5 344. piperidiny1 1-CH₃-2-imidazolyl
345. piperidiny1 2-CH₃-1-imidazolyl
346. piperidiny1 2-((CH₃)₂NCH₂)-1-imidazolyl
347. piperidiny1 2-((CH₃)NHCH₂)-1-imidazolyl
348. piperidiny1 2-((CH₃CH₂)NHCH₂)-1-imidazolyl
10 349. piperidiny1 2-((CH₃CH₂)₂NCH₂)-1-imidazolyl
350. piperidiny1 2-((CH₃CH₂)N(CH₃)CH₂)-1-imidazolyl
351. piperidiny1 2-(((CH₃)₂CH)NHCH₂)-1-imidazolyl
352. piperidiny1 2-(((CH₃)₂CH)₂NCH₂)-1-imidazolyl
353. piperidiny1 2-((cyclopropyl)NHCH₂)-1-imidazolyl
15 354. piperidiny1 2-((cyclopropyl)₂NCH₂)-1-imidazolyl
355. piperidiny1 2-((cyclobutyl)NHCH₂)-1-imidazolyl
356. piperidiny1 2-((cyclobutyl)₂NCH₂)-1-imidazolyl
357. piperidiny1 2-((cyclopentyl)NHCH₂)-1-imidazolyl
358. piperidiny1 2-((cyclopentyl)₂NCH₂)-1-imidazolyl
20 359. piperidiny1 2-((cyclohexyl)NHCH₂)-1-imidazolyl
360. piperidiny1 2-((cyclohexyl)₂NCH₂)-1-imidazolyl

25

Numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that within the scope of the appended claims, the invention may be practiced
30 otherwise that as specifically described herein.

WHAT IS CLAIMED IS:

1. A compound of formula Ia, Ib, or Ic:



or a stereoisomer or pharmaceutically acceptable salt thereof, wherein;

10 ring D₁ is selected from pyridine, pyrazine, pyridazine, and pyrimidine and is substituted with 1 R^a and 0-1 R^b;

ring D₂ is a 5-membered heteroaromatic ring system comprising E, carbon atoms, and 0-3 N atoms, wherein E
15 is selected from O, S, and N-R^c and ring D₂ is substituted with 1 R^a and 0-1 R^b;

ring D₃ is a 5-membered heteroaromatic ring system comprising carbon atoms and from 0-3 additional N atoms
20 and ring D₃ is substituted with 1 R^a and 0-1 R^b;

R is selected from H, C₁₋₄ alkyl, F, Cl, Br, I, OH, OCH₃, OCH₂CH₃, OCH(CH₃)₂, OCH₂CH₂CH₃, CN, C(=NR⁸)NR⁷R⁹, NHC(=NR⁸)NR⁷R⁹, NR⁸CH(=NR⁷), NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, C(=NH)NH₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), CH₂N(C₁₋₃ alkyl)₂, CH₂CH₂NH₂, CH₂CH₂NH(C₁₋₃ alkyl), CH₂CH₂N(C₁₋₃ alkyl)₂, (CR⁸R⁹)_tNR⁷R⁸, (CR⁸R⁹)_tC(O)NR⁷R⁸, and OCF₃;

25

R^a is selected from H, C₁₋₄ alkyl, F, Cl, Br, I, OH, OCH₃, OCH₂CH₃, OCH(CH₃)₂, OCH₂CH₂CH₃, CN, C(=NR⁸)NR⁷R⁹, NHC(=NR⁸)NR⁷R⁹, NR⁸CH(=NR⁷), NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, (CR⁸R⁹)_tNR⁷R⁸, (CR⁸R⁹)_tC(O)NR⁷R⁸, and OCF₃;

30

alkyl)₂, C(=NH)NH₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), CH₂N(C₁₋₃ alkyl)₂, CH₂CH₂NH₂, CH₂CH₂NH(C₁₋₃ alkyl), CH₂CH₂N(C₁₋₃ alkyl)₂, (CR⁸R⁹)_tNR⁷R⁸, (CR⁸R⁹)_tC(O)NR⁷R⁸, and OCF₃;

5 R^b is selected from H, C₁₋₄ alkyl, F, Cl, Br, I, OH, OCH₃, OCH₂CH₃, OCH(CH₃)₂, OCH₂CH₂CH₃, CN, C(=NR⁸)NR⁷R⁹, NHC(=NR⁸)NR⁷R⁹, NR⁸CH(=NR⁷), NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, C(=NH)NH₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), CH₂N(C₁₋₃ alkyl)₂, CH₂CH₂NH₂, CH₂CH₂NH(C₁₋₃ alkyl), CH₂CH₂N(C₁₋₃ alkyl)₂, (CR⁸R⁹)_tNR⁷R⁸, (CR⁸R⁹)_tC(O)NR⁷R⁸, and OCF₃;

R^c is selected from H, C₁₋₄ alkyl, OCH₃, OCH₂CH₃, OCH(CH₃)₂, OCH₂CH₂CH₃, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, C(=NH)NH₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), CH₂N(C₁₋₃ alkyl)₂, CH₂CH₂NH₂, CH₂CH₂NH(C₁₋₃ alkyl), CH₂CH₂N(C₁₋₃ alkyl)₂, (CR⁸R⁹)_tNR⁷R⁸, (CR⁸R⁹)_tC(O)NR⁷R⁸, and OCF₃;

G is absent or is selected from CH₂, C(O), O, NR³, S(O)_p, CH₂CH₂, C(O)CH₂, CH₂C(O), OCH₂, CH₂O, NR³CH₂, CH₂NR³, S(O)_pCH₂, CH₂S(O)_p, CH₂CH₂CH₂, C(O)CH₂CH₂, CH₂C(O)CH₂, CH₂CH₂C(O), OCH₂CH₂, CH₂OCH₂, CH₂CH₂O, NR³CH₂CH₂, CH₂NR³CH₂, CH₂CH₂NR³, S(O)_pCH₂CH₂, CH₂S(O)_pCH₂, and CH₂CH₂S(O)_p;

G₁ is absent or is selected from (CR³R^{3a})₁₋₅, (CR³R^{3a})₀₋₂CR³=CR³(CR³R^{3a})₀₋₂, (CR³R^{3a})₀₋₂C≡C(CR³R^{3a})₀₋₂, (CR³R^{3a})_uC(O)(CR³R^{3a})_w, (CR³R^{3a})_uC(O)O(CR³R^{3a})_w, (CR³R^{3a})_uOC(O)(CR³R^{3a})_w, (CR³R^{3a})_uO(CR³R^{3a})_w, (CR³R^{3a})_uNR³(CR³R^{3a})_w, (CR³R^{3a})_uC(O)NR³(CR³R^{3a})_w, (CR³R^{3a})_uNR³C(O)(CR³R^{3a})_w, (CR³R^{3a})_uOC(O)NR³(CR³R^{3a})_w, (CR³R^{3a})_uNR³C(O)O(CR³R^{3a})_w, (CR³R^{3a})_uNR³C(O)NR³(CR³R^{3a})_w, (CR³R^{3a})_uNR³C(S)NR³(CR³R^{3a})_w, (CR³R^{3a})_uS(CR³R^{3a})_w, (CR³R^{3a})_uS(O)(CR³R^{3a})_w, (CR³R^{3a})_uS(O)₂(CR³R^{3a})_w, (CR³R^{3a})_uS(O)NR³(CR³R^{3a})_w, (CR³R^{3a})_uNR³S(O)₂(CR³R^{3a})_w, (CR³R^{3a})_uS(O)₂NR³(CR³R^{3a})_w, and (CR³R^{3a})_uNR³S(O)₂NR³(CR³R^{3a})_w,

wherein $u + w$ total 0, 1, 2, 3, or 4, provided that G_1 does not form a N-N, N-O, N-S, NCH_2N , NCH_2O , or NCH_2S bond with either group to which it is attached;

5 G^2 is phenyl, naphthyl, or a 5-10 membered heteroaryl consisting of carbon atoms and from 1-3 heteroatoms selected from N, O, and S;

10 M is isoxazoline, pyrazoline, isothiazoline, triazoline, tetrazoline, phenyl, or a 5-6 membered aromatic heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from O, N, and S, and is substituted with -Z-A-B;

15 M is also substituted with 0-2 R^{1a} ;

Z is selected from a bond, $-(CR^2R^{2a})_{1-4}-$, $(CR^2R^{2a})_qO(CR^2R^{2a})_{q^1}$, $(CR^2R^{2a})_qNR^3(CR^2R^{2a})_{q^1}$, $(CR^2R^{2a})_qC(O)(CR^2R^{2a})_{q^1}$, $(CR^2R^{2a})_qC(O)O(CR^2R^{2a})_{q^1}$, $(CR^2R^{2a})_qOC(O)(CR^2R^{2a})_{q^1}$, $(CR^2R^{2a})_qC(O)NR^3(CR^2R^{2a})_{q^1}$, $(CR^2R^{2a})_qNR^3C(O)(CR^2R^{2a})_{q^1}$, $(CR^2R^{2a})_qOC(O)O(CR^2R^{2a})_{q^1}$, $(CR^2R^{2a})_qOC(O)NR^3(CR^2R^{2a})_{q^1}$, $(CR^2R^{2a})_qNR^3C(O)O(CR^2R^{2a})_{q^1}$, $(CR^2R^{2a})_qNR^3C(O)NR^3(CR^2R^{2a})_{q^1}$, $(CR^2R^{2a})_qS(CR^2R^{2a})_{q^1}$, $(CR^2R^{2a})_qS(O)(CR^2R^{2a})_{q^1}$, $(CR^2R^{2a})_qS(O)_2(CR^2R^{2a})_{q^1}$, $(CR^2R^{2a})_qSO_2NR^3(CR^2R^{2a})_{q^1}$, $(CR^2R^{2a})_qNR^3SO_2(CR^2R^{2a})_{q^1}$, and $(CR^2R^{2a})_qNR^3SO_2NR^3(CR^2R^{2a})_{q^1}$,
 20 wherein $q + q^1$ total 0, 1, or 2, provided that Z does not form a N-N, N-O, N-S, NCH_2N , NCH_2O , or NCH_2S bond with either group to which it is attached;

30 R^{1a} is selected from H, $-(CH_2)_r-R^{1b}$, $-CH=CH-R^{1b}$, NCH_2R^{1c} , OCH_2R^{1c} , SCH_2R^{1c} , $NH(CH_2)_2(CH_2)_tR^{1b}$, $O(CH_2)_2(CH_2)_tR^{1b}$, $S(CH_2)_2(CH_2)_tR^{1b}$, $S(O)_p(CH_2)_rR^{1d}$, $O(CH_2)_rR^{1d}$, $NR^3(CH_2)_rR^{1d}$, $OC(O)NR^3(CH_2)_rR^{1d}$, $NR^3C(O)NR^3(CH_2)_rR^{1d}$, $NR^3C(O)O(CH_2)_rR^{1d}$,

and $\text{NR}^3\text{C}(\text{O})(\text{CH}_2)_r\text{R}^{1d}$, provided that R^{1a} forms other than an N-halo, N-N, N-S, N-O, or N-CN bond;

alternatively, when two $\text{R}^{1a'}$'s are attached to adjacent atoms, together with the atoms to which they are attached they form a 5-7 membered ring consisting of: carbon atoms and 0-2 heteroatoms selected from the group consisting of N, O, and $\text{S}(\text{O})_p$, this ring being substituted with 0-2 R^{4b} and comprising: 0-3 double bonds;

R^{1b} is selected from H, C_{1-3} alkyl, F, Cl, Br, I, -CN, -CHO, $(\text{CF}_2)_r\text{CF}_3$, $(\text{CH}_2)_r\text{OR}^2$, NR^2R^{2a} , $\text{C}(\text{O})\text{R}^{2c}$, $\text{OC}(\text{O})\text{R}^2$, $(\text{CF}_2)_r\text{CO}_2\text{R}^{2a}$, $\text{S}(\text{O})_p\text{R}^{2b}$, $\text{NR}^2(\text{CH}_2)_r\text{OR}^2$, $\text{C}(=\text{NR}^{2c})\text{NR}^2\text{R}^{2a}$, $\text{NR}^2\text{C}(\text{O})\text{R}^{2b}$, $\text{NR}^2\text{C}(\text{O})\text{NHR}^{2b}$, $\text{NR}^2\text{C}(\text{O})_2\text{R}^{2a}$, $\text{OC}(\text{O})\text{NR}^{2a}\text{R}^{2b}$, $\text{C}(\text{O})\text{NR}^2\text{R}^{2a}$, $\text{C}(\text{O})\text{NR}^2(\text{CH}_2)_r\text{OR}^2$, $\text{SO}_2\text{NR}^2\text{R}^{2a}$, $\text{NR}^2\text{SO}_2\text{R}^{2b}$, C_{3-6} carbocycle substituted with 0-2 R^{4a} , and 5-10 membered heterocycle consisting of carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and $\text{S}(\text{O})_p$ substituted with 0-2 R^{4a} , provided that R^{1b} forms other than an N-halo, N-N, N-S, N-O, or N-CN bond;

R^{1c} is selected from H, $\text{CH}(\text{CH}_2\text{OR}^2)_2$, $\text{C}(\text{O})\text{R}^{2c}$, $\text{C}(\text{O})\text{NR}^2\text{R}^{2a}$, $\text{S}(\text{O})\text{R}^{2b}$, $\text{S}(\text{O})_2\text{R}^{2b}$, and $\text{SO}_2\text{NR}^2\text{R}^{2a}$;

R^{1d} is selected from C_{3-13} carbocycle substituted with 0-2 R^{4a} , and 5-13 membered heterocycle consisting of carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and $\text{S}(\text{O})_p$ substituted with 0-2 R^{4a} , provided that R^{1d} forms other than an N-N, N-S, or N-O bond;

R^2 , at each occurrence, is selected from H, CF_3 , C_{1-6} alkyl, benzyl, C_{3-6} carbocyclic residue substituted with 0-2

R^{4b}, and 5-6 membered heterocyclic system comprising carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

5

R^{2a}, at each occurrence, is selected from H, CF₃, C₁₋₆ alkyl, benzyl, phenethyl, C₃₋₆ carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system comprising carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

10

R^{2b}, at each occurrence, is selected from CF₃, C₁₋₄ alkoxy, C₁₋₆ alkyl, benzyl, C₃₋₆ carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system comprising carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

15

R^{2c}, at each occurrence, is selected from CF₃, OH, C₁₋₄ alkoxy, C₁₋₆ alkyl, benzyl, C₃₋₆ carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system comprising carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

20
25

alternatively, R² and R^{2a}, together with the atom to which they are attached, combine to form a 5 or 6 membered saturated, partially saturated or unsaturated ring substituted with 0-2 R^{4b} and comprising carbon atoms and from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;

30

R^3 , at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

5 R^{3a} , at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

R^{3b} , at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

10 R^{3c} , at each occurrence, is selected from C_{1-4} alkyl, and phenyl;

R^{3d} , at each occurrence, is selected from H, C_{1-4} alkyl, C_{1-4} alkyl-phenyl, and $C(=O)R^{3c}$;

15

A is selected from:

C_{3-10} carbocyclic residue substituted with 0-2 R^4 , and 5-12 membered heterocyclic system comprising carbon atoms and from 1-4 heteroatoms selected from the group
20 consisting of N, O, and S substituted with 0-2 R^4 ;

B is selected from: H, Y, and X-Y, provided that Z and B -are attached to different atoms on A;

25 X is selected from $-(CR^2R^{2a})_{1-4}-$, $-CR^2(CR^2R^{2b})(CH_2)_t-$, $-C(O)-$, $-C(=NR^{1c})-$, $-CR^2(NR^{1c}R^2)-$, $-CR^2(OR^2)-$, $-CR^2(SR^2)-$, $-C(O)CR^2R^{2a}-$, $-CR^2R^{2a}C(O)-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-SCR^2R^{2a}-$, $-S(O)CR^2R^{2a}-$, $-S(O)_2CR^2R^{2a}-$, $-CR^2R^{2a}S-$, $-CR^2R^{2a}S(O)-$, $-CR^2R^{2a}S(O)_2-$, $-S(O)_2NR^2-$, $-NR^2S(O)_2-$,
30 $-NR^2S(O)_2CR^2R^{2a}-$, $-CR^2R^{2a}S(O)_2NR^2-$, $-NR^2S(O)_2NR^2-$, $-C(O)NR^2-$, $-NR^2C(O)-$, $-C(O)NR^2CR^2R^{2a}-$, $-NR^2C(O)CR^2R^{2a}-$, $-CR^2R^{2a}C(O)NR^2-$, $-CR^2R^{2a}NR^2C(O)-$, $-NR^2C(O)O-$, $-OC(O)NR^2-$,

$-\text{NR}^2\text{C}(\text{O})\text{NR}^2-$, $-\text{NR}^2-$, $-\text{NR}^2\text{CR}^2\text{R}^{2a}-$, $-\text{CR}^2\text{R}^{2a}\text{NR}^2-$, O ,
 $-\text{CR}^2\text{R}^{2a}\text{O}-$, and $-\text{OCR}^2\text{R}^{2a}-$;

Y is selected from:

5 C_{3-10} carbocyclic residue substituted with 0-2 R^{4a} , and
 5-12 membered heterocyclic system comprising carbon
 atoms and from 1-4 heteroatoms selected from the group
 consisting of N, O, and S substituted with 0-2 R^{4a} ;

10 R^4 , at each occurrence, is selected from H, $=\text{O}$, $(\text{CH}_2)_r\text{OR}^2$,
 $(\text{CH}_2)_r\text{F}$, $(\text{CH}_2)_r\text{Cl}$, $(\text{CH}_2)_r\text{Br}$, $(\text{CH}_2)_r\text{I}$, C_{1-4} alkyl,
 $(\text{CH}_2)_r\text{CN}$, $(\text{CH}_2)_r\text{NO}_2$, $(\text{CH}_2)_r\text{NR}^2\text{R}^{2a}$, $\text{C}(\text{O})\text{R}^{2c}$, $\text{NR}^2\text{C}(\text{O})\text{R}^{2b}$,
 $\text{C}(\text{O})\text{NR}^2\text{R}^{2a}$, $\text{NR}^2\text{C}(\text{O})\text{NR}^2\text{R}^{2a}$, $\text{C}(=\text{NR}^2)\text{NR}^2\text{R}^{2a}$,
 $\text{C}(=\text{NS}(\text{O})_2\text{R}^5)\text{NR}^2\text{R}^{2a}$, $\text{NHC}(=\text{NR}^2)\text{NR}^2\text{R}^{2a}$, $\text{C}(\text{O})\text{NHC}(=\text{NR}^2)\text{NR}^2\text{R}^{2a}$,
 15 $\text{SO}_2\text{NR}^2\text{R}^{2a}$, $\text{NR}^2\text{SO}_2\text{NR}^2\text{R}^{2a}$, $\text{NR}^2\text{SO}_2-\text{C}_{1-4}$ alkyl, $\text{NR}^2\text{SO}_2\text{R}^5$,
 $\text{S}(\text{O})_p\text{R}^5$, $(\text{CF}_2)_r\text{CF}_3$, $(\text{CH}_2)_r-\text{CF}_3$, $\text{NCH}_2\text{R}^{1c}$, $\text{OCH}_2\text{R}^{1c}$, $\text{SCH}_2\text{R}^{1c}$,
 $\text{N}(\text{CH}_2)_2(\text{CH}_2)_t\text{R}^{1b}$, $\text{O}(\text{CH}_2)_2(\text{CH}_2)_t\text{R}^{1b}$, $\text{S}(\text{CH}_2)_2(\text{CH}_2)_t\text{R}^{1b}$, 5-6
 membered carbocycle substituted with 0-1 R^5 , and 5-6
 membered heterocycle consisting of: carbon atoms and
 20 1-4 heteroatoms selected from the group consisting of
 N, O, and $\text{S}(\text{O})_p$ substituted with 0-1 R^5 ;

R^{4a} , at each occurrence, is selected from H, $=\text{O}$, $(\text{CH}_2)_r\text{OR}^2$,
 $(\text{CF}_2)_r\text{CF}_3$, $(\text{CH}_2)_r-\text{CF}_3$, $(\text{CH}_2)_r-\text{F}$, $(\text{CH}_2)_r-\text{Br}$, $(\text{CH}_2)_r-\text{Cl}$,
 25 C_{1-4} alkyl, $(\text{CH}_2)_r\text{CN}$, $(\text{CH}_2)_r\text{NO}_2$, $(\text{CH}_2)_r\text{NR}^2\text{R}^{2a}$,
 $(\text{CH}_2)_r\text{C}(\text{O})\text{R}^{2c}$, $\text{NR}^2\text{C}(\text{O})\text{R}^{2b}$, $\text{C}(\text{O})\text{NR}^2\text{R}^{2a}$, $(\text{CH}_2)_r\text{N}=\text{CHOR}^3$,
 $\text{C}(\text{O})\text{NH}(\text{CH}_2)_2\text{NR}^2\text{R}^{2a}$, $\text{NR}^2\text{C}(\text{O})\text{NR}^2\text{R}^{2a}$, $\text{C}(=\text{NR}^2)\text{NR}^2\text{R}^{2a}$,
 $\text{NHC}(=\text{NR}^2)\text{NR}^2\text{R}^{2a}$, $\text{SO}_2\text{NR}^2\text{R}^{2a}$, $\text{NR}^2\text{SO}_2\text{NR}^2\text{R}^{2a}$, $\text{NR}^2\text{SO}_2-\text{C}_{1-4}$
 alkyl, $\text{NR}^2\text{SO}_2\text{R}^5$, $\text{C}(\text{O})\text{NHSO}_2-\text{C}_{1-4}$ alkyl, $\text{S}(\text{O})_p\text{R}^5$, 5-6
 30 membered carbocycle substituted with 0-1 R^5 , and 5-6
 membered heterocycle consisting of: carbon atoms and
 1-4 heteroatoms selected from the group consisting of
 N, O, and $\text{S}(\text{O})_p$ substituted with 0-1 R^5 ;

- R^{4b} , at each occurrence, is selected from H, =O, $(CH_2)_rOR^3$,
 $(CH_2)_r-F$, $(CH_2)_r-Cl$, $(CH_2)_r-Br$, $(CH_2)_r-I$, C_{1-4} alkyl,
 $(CH_2)_r-CN$, $(CH_2)_r-NO_2$, $(CH_2)_rNR^3R^{3a}$, $(CH_2)_rC(O)R^3$,
5 $(CH_2)_rC(O)OR^{3c}$, $NR^3C(O)R^{3a}$, $C(O)NR^3R^{3a}$, $NR^3C(O)NR^3R^{3a}$,
 $C(=NR^3)NR^3R^{3a}$, $NR^3C(=NR^3)NR^3R^{3a}$, $SO_2NR^3R^{3a}$, $NR^3SO_2NR^3R^{3a}$,
 $NR^3SO_2-C_{1-4}$ alkyl, $NR^3SO_2CF_3$, NR^3SO_2 -phenyl, $S(O)_pCF_3$,
 $S(O)_p-C_{1-4}$ alkyl, $S(O)_p$ -phenyl, $(CH_2)_rCF_3$, and $(CF_2)_rCF_3$;
- 10 R^5 , at each occurrence, is selected from H, C_{1-6} alkyl, =O,
 $(CH_2)_rOR^3$, F, Cl, Br, I, -CN, NO_2 , $(CH_2)_rNR^3R^{3a}$,
 $(CH_2)_rC(O)R^3$, $(CH_2)_rC(O)OR^{3c}$, $NR^3C(O)R^{3a}$, $C(O)NR^3R^{3a}$,
 $NR^3C(O)NR^3R^{3a}$, $CH(=NOR^{3d})$, $C(=NR^3)NR^3R^{3a}$,
 $NR^3C(=NR^3)NR^3R^{3a}$, $SO_2NR^3R^{3a}$, $NR^3SO_2NR^3R^{3a}$, $NR^3SO_2-C_{1-4}$
15 alkyl, $NR^3SO_2CF_3$, NR^3SO_2 -phenyl, $S(O)_pCF_3$, $S(O)_p-C_{1-4}$
alkyl, $S(O)_p$ -phenyl, $(CF_2)_rCF_3$, phenyl substituted with
0-2 R^6 , naphthyl substituted with 0-2 R^6 , and benzyl
substituted with 0-2 R^6 ;
- 20 R^6 , at each occurrence, is selected from H, OH, $(CH_2)_rOR^2$,
halo, C_{1-4} alkyl, CN, NO_2 , $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2b}$,
 $NR^2C(O)R^{2b}$, $NR^2C(O)NR^2R^{2a}$, $C(=NH)NH_2$, $NHC(=NH)NH_2$,
 $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, and $NR^2SO_2C_{1-4}$ alkyl;
- 25 R^7 , at each occurrence, is selected from H, OH, C_{1-4}
alkoxycarbonyl, C_{6-10} aryloxy, C_{6-10} aryloxycarbonyl,
 C_{6-10} arylmethylcarbonyl, C_{1-4} alkylcarbonyloxy C_{1-4}
alkoxycarbonyl, C_{6-10} arylcarbonyloxy C_{1-4}
alkoxycarbonyl, C_{1-6} alkylaminocarbonyl,
30 phenylaminocarbonyl, and phenyl C_{1-4} alkoxycarbonyl;

R^8 , at each occurrence, is selected from H, C_{1-6} alkyl, and $(CH_2)_n$ -phenyl;

alternatively, R^7 and R^8 , when attached to the same nitrogen,
 5 combine to form a 5-6 membered heterocyclic ring
 consisting of carbon atoms and 0-2 additional
 heteroatoms selected from the group consisting of N, O,
 and $S(O)_p$;

10 R^9 , at each occurrence, is selected from H, C_{1-6} alkyl, and $(CH_2)_n$ -phenyl;

n , at each occurrence, is selected from 0, 1, 2, and 3;

15 m , at each occurrence, is selected from 0, 1, and 2;

p , at each occurrence, is selected from 0, 1, and 2;

r , at each occurrence, is selected from 0, 1, 2, and 3;

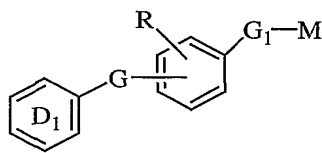
20

s , at each occurrence, is selected from 0, 1, and 2; and,

t , at each occurrence, is selected from 0, 1, 2, and 3.

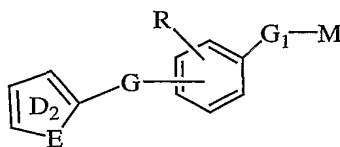
25

2. A compound according to Claim 1, wherein the
 compound is of formula Ia₁-Ic₁, wherein:

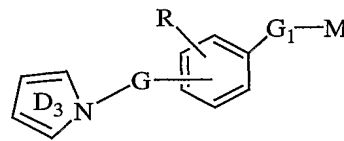


30

Ia₁



Ib₁



Ic₁

ring D₂ is a 5-membered heteroaromatic ring system comprising E, carbon atoms, and 0-2 N atoms, wherein E is selected from O, S, and N-R^c and ring D₂ is substituted with 1 R^a and 0-1 R^b;

5

ring D₃ is a 5-membered heteroaromatic ring system comprising carbon atoms and from 0-3 additional N atoms and ring D₃ is substituted with 1 R^a and 0-1 R^b;

10 R is selected from H, Cl, F, Br, I, OH, C₁₋₃ alkoxy, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), CH₂N(C₁₋₃ alkyl)₂, CH₂CH₂NH₂, CH₂CH₂NH(C₁₋₃ alkyl), and CH₂CH₂N(C₁₋₃ alkyl)₂;

15 R^a is selected from H, OH, SH, C₁₋₃ alkoxy, C₁₋₃ thioalkoxy, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), CH₂N(C₁₋₃ alkyl)₂, CH₂CH₂NH₂, CH₂CH₂NH(C₁₋₃ alkyl), and CH₂CH₂N(C₁₋₃ alkyl)₂;

20 R^b is selected from H, C₁₋₄ alkyl, Cl, F, Br, I, OH, C₁₋₃ alkoxy, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), CH₂N(C₁₋₃ alkyl)₂, CH₂CH₂NH₂, CH₂CH₂NH(C₁₋₃ alkyl), and CH₂CH₂N(C₁₋₃ alkyl)₂;

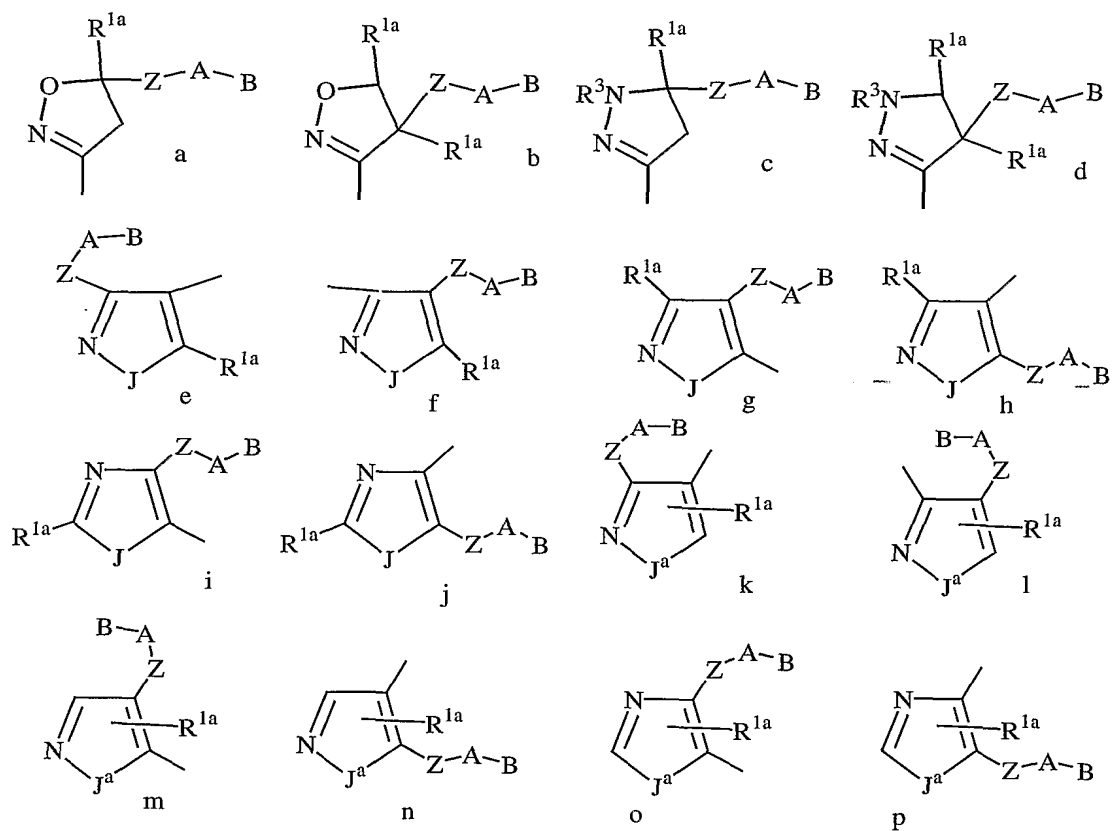
25 R^c is selected from H, C₁₋₄ alkyl, C₁₋₃ alkoxy, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), CH₂N(C₁₋₃ alkyl)₂, CH₂CH₂NH₂, CH₂CH₂NH(C₁₋₃ alkyl), and CH₂CH₂N(C₁₋₃ alkyl)₂;

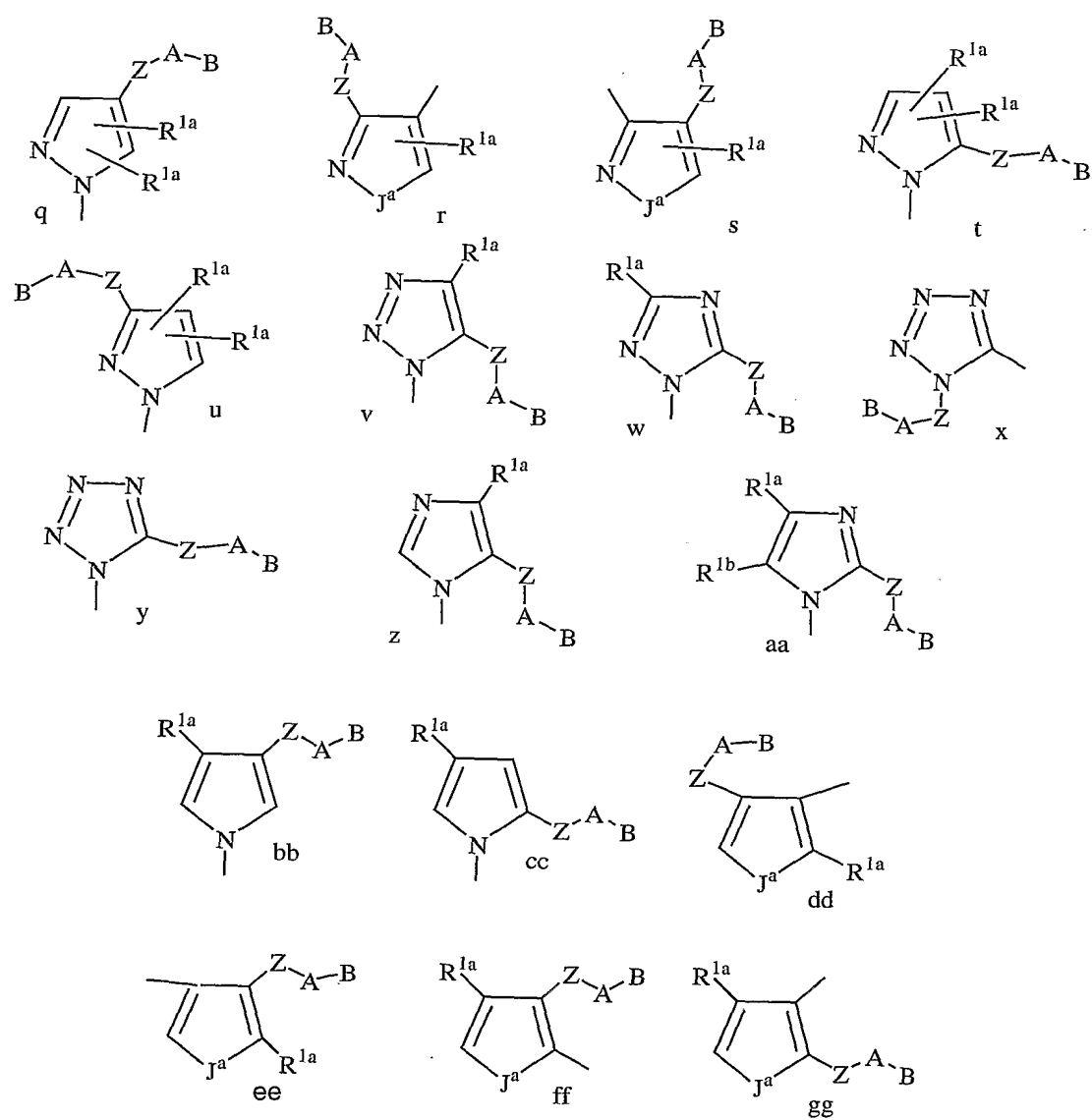
30 G₁ is absent or is selected from CH₂, C(O), O, NR³, S(O)_p, CH₂CH₂, C(O)CH₂, CH₂C(O), OCH₂, CH₂O, NR³CH₂, CH₂NR³, S(O)_pCH₂, CH₂S(O)_p, CH₂CH₂CH₂, C(O)CH₂CH₂, CH₂C(O)CH₂, CH₂CH₂C(O), OCH₂CH₂, CH₂OCH₂, CH₂CH₂O, NR³CH₂CH₂, CH₂NR³CH₂, CH₂CH₂NR³, S(O)_pCH₂CH₂, CH₂S(O)_pCH₂, and CH₂CH₂S(O)_p, and

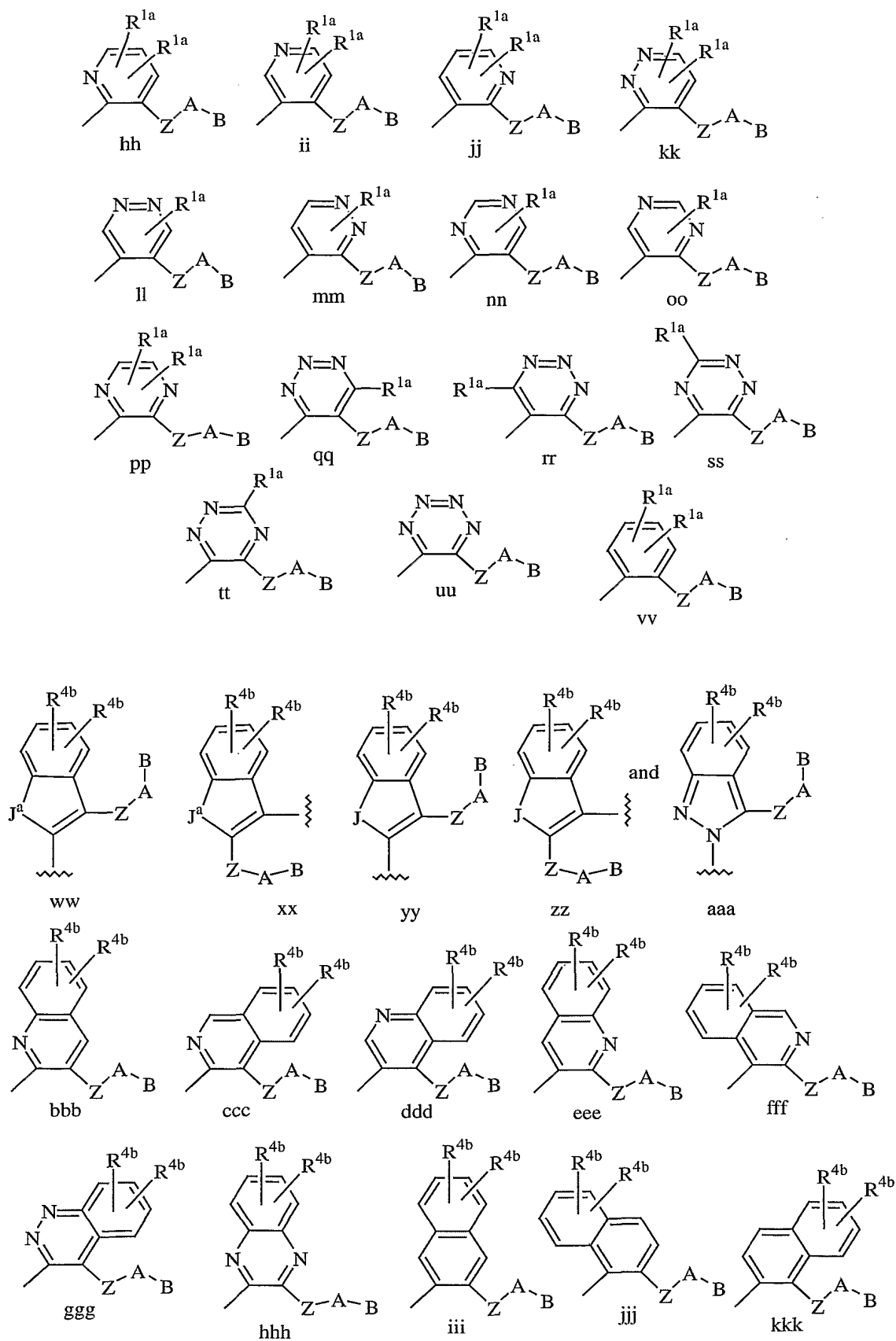
provided that G_1 -M form other than a N-N, O-N, or S-N bond;

M is selected from the group:

5







J is O or S;

J^a is NH or NR^{1a};

5

G₁ is absent or is selected from (CR³R^{3a})₁₋₃,

(CR³R^{3a})_uC(O)(CR³R^{3a})_w, (CR³R^{3a})_uO(CR³R^{3a})_w,

(CR³R^{3a})_uNR³(CR³R^{3a})_w, (CR³R^{3a})_uC(O)NR³(CR³R^{3a})_w,

(CR³R^{3a})_uNR³C(O)(CR³R^{3a})_w, (CR³R^{3a})_uS(CR³R^{3a})_w,

10 (CR³R^{3a})_uS(O)(CR³R^{3a})_w, (CR³R^{3a})_uS(O)₂(CR³R^{3a})_w,

(CR³R^{3a})_uS(O)NR³(CR³R^{3a})_w, and (CR³R^{3a})_uS(O)₂NR³(CR³R^{3a})_w,

wherein u + w total 0, 1, or 2, provided that G₁ does not form a N-N, N-O, N-S, NCH₂N, NCH₂O, or NCH₂S bond with either group to which it is attached;

15

A is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R⁴;

phenyl, piperidinyl, piperazinyl, pyridyl,

pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl,

20 pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl,

isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl,

thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl,

1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl,

1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl,

25 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl,

1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl,

1,2,5-triazolyl, 1,3,4-triazolyl, benzofuranyl,

benzothiofuranyl, indolyl, benzimidazolyl,

benzoxazolyl, benzthiazolyl, indazolyl, benzisoxazolyl,

30 benzisothiazolyl, and isoindazolyl;

X is selected from -(CR²R^{2a})₁₋₄-, -C(O)-, -C(=NR^{1c})-,

-CR²(NR^{1c}R²)-, -C(O)CR²R^{2a}-, -CR²R^{2a}C(O)-, -C(O)NR²-,

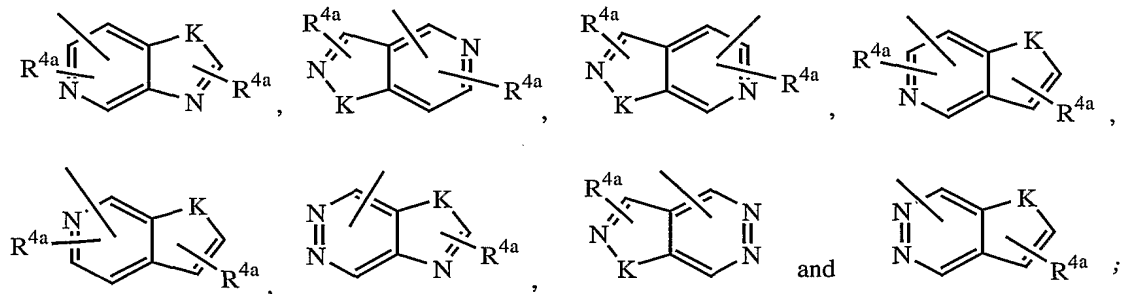
-NR²C(O)-, -C(O)NR²CR²R^{2a}-, -NR²C(O)CR²R^{2a}-,

$-\text{CR}^2\text{R}^{2a}\text{C}(\text{O})\text{NR}^2-$, $-\text{CR}^2\text{R}^{2a}\text{NR}^2\text{C}(\text{O})-$, $-\text{NR}^2\text{C}(\text{O})\text{NR}^2-$, $-\text{NR}^2-$,
 $-\text{NR}^2\text{CR}^2\text{R}^{2a}-$, $-\text{CR}^2\text{R}^{2a}\text{NR}^2-$, O , $-\text{CR}^2\text{R}^{2a}\text{O}-$, and $-\text{OCR}^2\text{R}^{2a}-$;

Y is selected from one of the following carbocyclic and

5 heterocyclic systems that are substituted with 0-2 R^{4a} ;
 cyclopropyl, cyclopentyl, cyclohexyl, phenyl,
 piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl,
 morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl,
 oxazolyl, isoxazolyl, isoxazolinyl, thiazolyl,
 10 isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl,
 thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl,
 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl,
 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl,
 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl,
 15 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl,
 1,2,5-triazolyl, 1,3,4-triazolyl, benzofuranyl,
 benzothiofuranyl, indolyl, benzimidazolyl,
 benzoxazolyl, benzthiazolyl, indazolyl, benzisoxazolyl,
 benzisothiazolyl, and isoindazolyl;

20 alternatively, Y is selected from the following bicyclic
 heteroaryl ring systems:



25 K is selected from O, S, NH, and N;

Z is selected from a bond, CH_2O , OCH_2 , NH , CH_2NH , NHCH_2 ,
 $\text{CH}_2\text{C}(\text{O})$, $\text{C}(\text{O})\text{CH}_2$, $\text{C}(\text{O})\text{NH}$, $\text{NHC}(\text{O})$, $\text{CH}_2\text{S}(\text{O})_2$, $\text{S}(\text{O})_2(\text{CH}_2)$,
 SO_2NH , and NHSO_2 , provided that Z does not form a N-N,

N-O, N-S, NCH₂N, NCH₂O, or NCH₂S bond with either group to which it is attached;

- 5 R⁴, at each occurrence, is selected from H, =O, (CH₂)_rOR², F, Cl, Br, I, C₁₋₄ alkyl, CN, NO₂, (CH₂)_rNR²R^{2a}, C(O)R^{2c}, NR²C(O)R^{2b}, C(O)NR²R^{2a}, NR²C(O)NR²R^{2a}, C(=NR²)NR²R^{2a}, SO₂NR²R^{2a}, NR²SO₂NR²R^{2a}, NR²SO₂-C₁₋₄ alkyl, NR²SO₂R⁵, S(O)_pR⁵, CF₃, NCH₂R^{1c}, OCH₂R^{1c}, SCH₂R^{1c}, N(CH₂)₂(CH₂)_tR^{1b}, O(CH₂)₂(CH₂)_tR^{1b}, S(CH₂)₂(CH₂)_tR^{1b}, 5-6 membered
- 10 carbocycle substituted with 0-1 R⁵, and 5-6 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)_p substituted with 0-1 R⁵; and,
- 15 R^{4a}, at each occurrence, is selected from H, =O, (CH₂)_rOR², CF₃, F, Br, Cl, C₁₋₄ alkyl, CN, NO₂, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c}, NR²C(O)R^{2b}, C(O)NR²R^{2a}, NR²C(O)NR²R^{2a}, C(=NR²)NR²R^{2a}, NHC(=NR²)NR²R^{2a}, SO₂NR²R^{2a}, NR²SO₂NR²R^{2a}, NR²SO₂-C₁₋₄ alkyl, NR²SO₂R⁵, C(O)NHSO₂-C₁₋₄ alkyl,
- 20 S(O)_pR⁵, 5-6 membered carbocycle substituted with 0-1 R⁵, and 5-6 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)_p substituted with 0-1 R⁵.

25

3. A compound according to Claim 2, wherein the compound is of formula Ib₁ or Ic₁, wherein:

- ring D₂ is a 5-membered heteroaromatic ring system
- 30 comprising E, carbon atoms, and 0-2 N atoms, wherein E is selected from O, S, and N-R^c and ring D₂ is substituted with 1 R^a and 0-1 R^b;

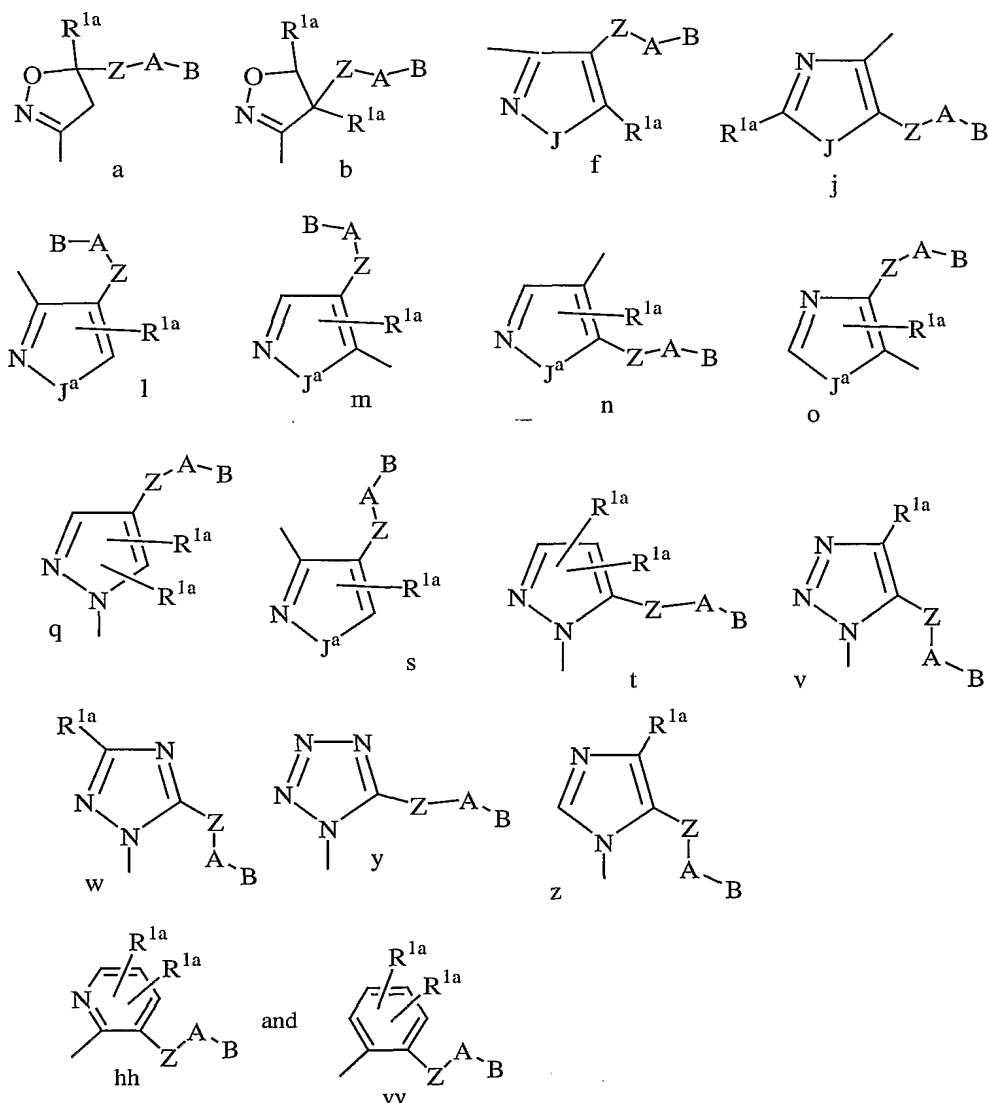
R is selected from H, Cl, F, Br, I, OH, C₁₋₃ alkoxy, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), and CH₂N(C₁₋₃ alkyl)₂;

5 R^a is selected from H, OH, SH, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), and CH₂N(C₁₋₃ alkyl)₂;

10 R^b is selected from H, C₁₋₄ alkyl, Cl, F, Br, I, OH, C₁₋₃ alkoxy, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), and CH₂N(C₁₋₃ alkyl)₂;

15 R^c is selected from H, C₁₋₄ alkyl, C₁₋₃ alkoxy, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), and CH₂N(C₁₋₃ alkyl)₂;

M is selected from the group:



Y is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R^{4a} ;

5 phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazole, thiadiazole, triazole, 1,2,3-oxadiazole, 1,2,4-

10 oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, 1,3,4-thiadiazole, 1,2,3-triazole, 1,2,4-triazole, 1,2,5-triazole, 1,3,4-triazole, benzofuran,

benzothiofuran, indole, benzimidazole, benzimidazolone, benzoxazole, benzthiazole, indazole, benzisoxazole, benzisothiazole, and isoindazole;

5 Z is selected from a bond, CH_2O , OCH_2 , NH , CH_2NH , NHCH_2 , $\text{CH}_2\text{C}(\text{O})$, $\text{C}(\text{O})\text{CH}_2$, $\text{C}(\text{O})\text{NH}$, $\text{NHC}(\text{O})$, $\text{CH}_2\text{S}(\text{O})_2$, $\text{S}(\text{O})_2(\text{CH}_2)$, SO_2NH , and NHSO_2 , provided that Z does not form a N-N, N-O, N-S, NCH_2N , NCH_2O , or NCH_2S bond with either group to which it is attached;

10

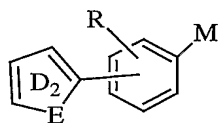
R^4 , at each occurrence, is selected from H, $=\text{O}$, $(\text{CH}_2)_r\text{OR}^2$, F, Cl, Br, I, C_{1-4} alkyl, CN, NO_2 , $(\text{CH}_2)_r\text{NR}^2\text{R}^{2a}$, $\text{C}(\text{O})\text{R}^{2c}$, $\text{NR}^2\text{C}(\text{O})\text{R}^{2b}$, $\text{C}(\text{O})\text{NR}^2\text{R}^{2a}$, $\text{NR}^2\text{C}(\text{O})\text{NR}^2\text{R}^{2a}$, $\text{C}(=\text{NR}^2)\text{NR}^2\text{R}^{2a}$, $\text{SO}_2\text{NR}^2\text{R}^{2a}$, $\text{NR}^2\text{SO}_2\text{NR}^2\text{R}^{2a}$, $\text{NR}^2\text{SO}_2\text{-C}_{1-4}$ alkyl, $\text{NR}^2\text{SO}_2\text{R}^5$, $\text{S}(\text{O})_p\text{R}^5$, CF_3 , 5-6 membered carbocycle substituted with 0-1 R^5 , and 5-6 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $\text{S}(\text{O})_p$ substituted with 0-1 R^5 ; and,

20

R^{4a} , at each occurrence, is selected from H, $=\text{O}$, $(\text{CH}_2)_r\text{OR}^2$, CF_3 , F, Br, Cl, C_{1-4} alkyl, CN, NO_2 , $(\text{CH}_2)_r\text{NR}^2\text{R}^{2a}$, $(\text{CH}_2)_r\text{C}(\text{O})\text{R}^{2c}$, $\text{NR}^2\text{C}(\text{O})\text{R}^{2b}$, $\text{C}(\text{O})\text{NR}^2\text{R}^{2a}$, $\text{NR}^2\text{C}(\text{O})\text{NR}^2\text{R}^{2a}$, $\text{C}(=\text{NR}^2)\text{NR}^2\text{R}^{2a}$, $\text{SO}_2\text{NR}^2\text{R}^{2a}$, $\text{C}(\text{O})\text{NHSO}_2\text{-C}_{1-4}$ alkyl, $\text{S}(\text{O})_p\text{R}^5$, 5-6 membered carbocycle substituted with 0-1 R^5 , and 5-6 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $\text{S}(\text{O})_p$ substituted with 0-1 R^5 .

30

4. A compound according to Claim 3, wherein the compound is of formula Ib_2 :

Ib₂

or a stereoisomer or pharmaceutically acceptable salt thereof, wherein;

5

ring D₂ is a 5-membered heteroaromatic ring system comprising E, carbon atoms, and 0-2 N atoms, wherein E is selected from O, S, and N-R^C and ring D₂ is substituted with 1 R^a and 0-1 R^b;

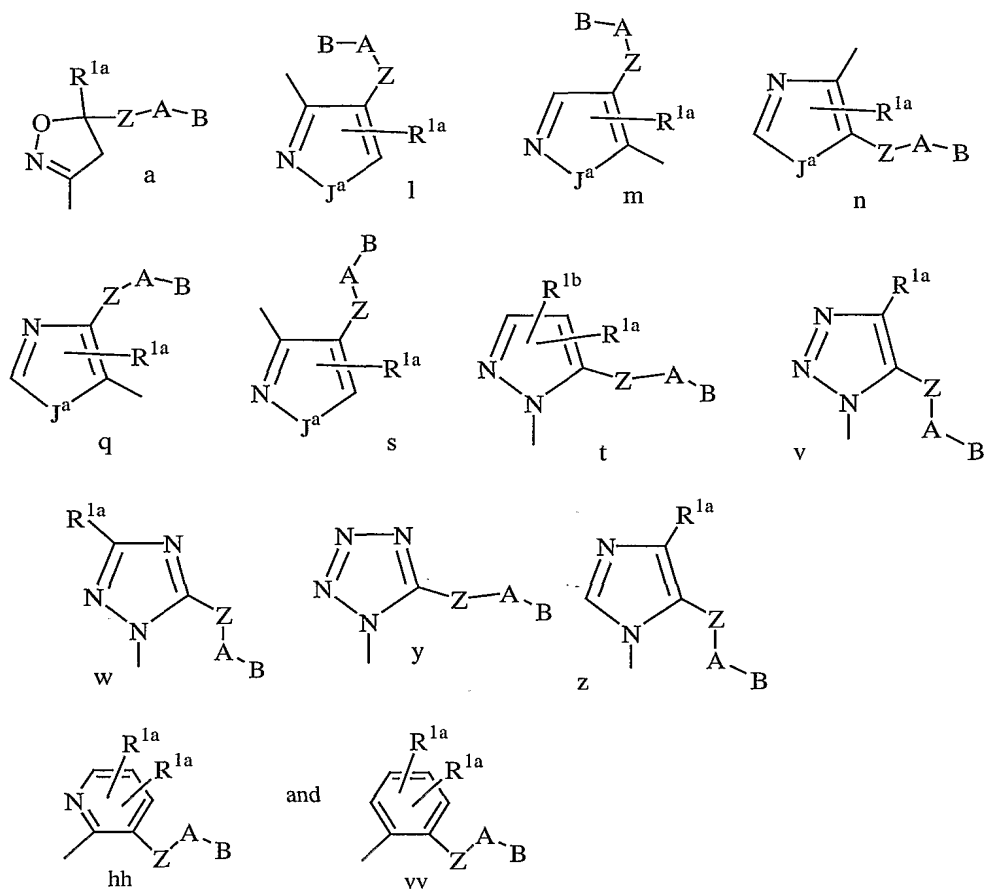
10

R is selected from H, Cl, F, Br, I, OH, C₁₋₃ alkoxy, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, CH₂NH₂, CH₂NH(C₁₋₃ alkyl), and CH₂N(C₁₋₃ alkyl)₂;

15 R^a is selected from H, OH, SH, NH₂, NH(C₁₋₃ alkyl), and N(C₁₋₃ alkyl)₂;

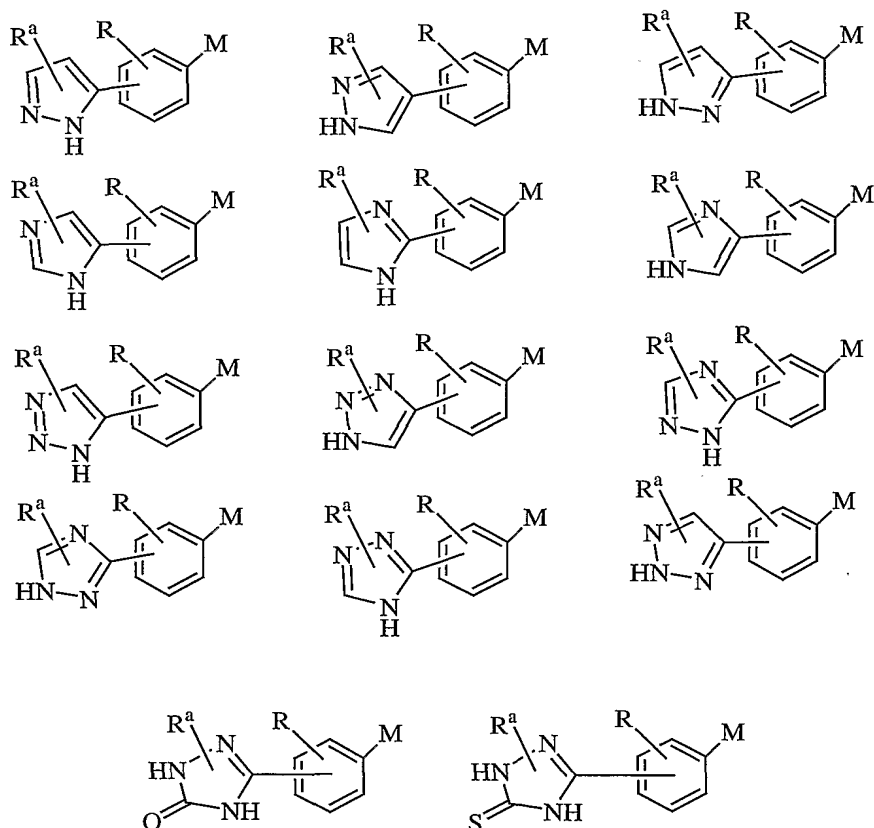
R^b is selected from H, C₁₋₄ alkyl, Cl, F, Br, I, OH, C₁₋₃ alkoxy, NH₂, NH(C₁₋₃ alkyl), N(C₁₋₃ alkyl)₂, CH₂NH₂,
20 CH₂NH(C₁₋₃ alkyl), and CH₂N(C₁₋₃ alkyl)₂;

M is selected from the group:



G_1 is absent or is selected from CH_2 , CH_2CH_2 , CH_2O , OCH_2 , NH , CH_2NH , $NHCH_2$, $CH_2C(O)$, $C(O)CH_2$, $C(O)NH$, $NHC(O)$, $CH_2S(O)_2$, $S(O)_2(CH_2)$, SO_2NH , and $NHSO_2$, provided that G_1 does not form a N-N, N-O, N-S, NCH_2N , NCH_2O , or NCH_2S bond with either group to which it is attached.

- 10 5. A compound according to Claim 4, wherein the compound is selected from one of the formulas:



5 or a stereoisomer or pharmaceutically acceptable salt thereof, wherein;

G_1 is absent;

10 A is selected from phenyl, piperidinyl, pyridyl, and pyrimidyl, and is substituted with 0-2 R^4 ; and,

B is selected from phenyl, pyrrolidino, N-pyrrolidino-carbonyl, morpholino, N-morpholino-carbonyl, 1,2,3-
 15 triazolyl, imidazolyl, and benzimidazolyl, and is substituted with 0-1 R^{4a} ;

R^2 , at each occurrence, is selected from H, CH_3 , CH_2CH_3 , cyclopropylmethyl, cyclobutyl, and cyclopentyl;

20

R^{2a}, at each occurrence, is selected from H, CH₃, and CH₂CH₃;

alternatively, R² and R^{2a}, together with the atom to which they are attached, combine to form pyrrolidine

5 substituted with 0-2 R^{4b} or piperidine substituted with 0-2 R^{4b};

R⁴, at each occurrence, is selected from OH, OR², (CH₂)OR², (CH₂)₂OR², F, Br, Cl, I, C₁₋₄ alkyl, NR²R^{2a}, (CH₂)NR²R^{2a}, 10 (CH₂)₂NR²R^{2a}, CF₃, and (CF₂)CF₃;

R^{4a} is selected from C₁₋₄ alkyl, CF₃, OR², (CH₂)OR², (CH₂)₂OR², NR²R^{2a}, (CH₂)NR²R^{2a}, (CH₂)₂NR²R^{2a}, SR⁵, S(O)R⁵, S(O)₂R⁵, SO₂NR²R^{2a}, and 1-CF₃-tetrazol-2-yl;

15

R^{4b}, at each occurrence, is selected from H, CH₃, and OH;

R⁵, at each occurrence, is selected from CF₃, C₁₋₆ alkyl, phenyl, and benzyl; and,

20

r, at each occurrence, is selected from 0, 1, and 2.

6. A compound according to Claim 5, wherein:

25

A is selected from the group: phenyl, piperidinyl, 2-pyridyl, 3-pyridyl, 2-pyrimidyl, 2-Cl-phenyl, 3-Cl-phenyl, 2-F-phenyl, 3-F-phenyl, 2-methylphenyl, 2-aminophenyl, and 2-methoxyphenyl; and,

30

B is selected from the group: 2-(aminosulfonyl)phenyl, 2-(methylaminosulfonyl)phenyl, 1-pyrrolidinocarbonyl, 2-(methylsulfonyl)phenyl, 2-(N,N-dimethylaminomethyl)phenyl, 2-(N-

methyaminomethyl)phenyl, 2-(N-ethyl-N-methyaminomethyl)phenyl, 2-(N-pyrrolidinylmethyl)phenyl, 1-methyl-2-imidazolyl, 2-methyl-1-imidazolyl, 2-(dimethylaminomethyl)-1-imidazolyl, 2-(methyaminomethyl)-1-imidazolyl, 2-(N-(cyclopropylmethyl)aminomethyl)phenyl, 2-(N-(cyclobutyl)aminomethyl)phenyl, 2-(N-(cyclopentyl)aminomethyl)phenyl, 2-(N-(4-hydroxypiperidinyl)methyl)phenyl, and 2-(N-(3-hydroxypyrrolidinyl)methyl)phenyl.

7. A compound according to Claim 1, wherein the compound is selected from the group:

- 15 1-[3-(1',3',4'-Triazol-2'-on-5'-yl)phenyl]-3-trifluoromethyl-5-[(2'-N,N-dimethylaminomethyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole;
- 20 1-[3-(1',3',4'-Triazol-2'-on-5'-yl)phenyl]-3-trifluoromethyl-5-[(2'-N-pyrrolidinylmethyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole;
- 25 1-[3-(1',3',4'-Triazol-2'-on-5'-yl)phenyl]-3-trifluoromethyl-5-[(3-fluoro-2'-N,N-dimethylaminomethyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole;
- 30 1-[3-(1',3',4'-Triazol-2'-on-5'-yl)phenyl]-3-trifluoromethyl-5-[(3-fluoro-2'-N-pyrrolidinylmethyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole;
- 35 1-[3-(1',3',4'-Triazol-2'-on-5'-yl)phenyl]-3-trifluoromethyl-5-[(2'-sulfonylmethyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole;

1-[3-(1',3',4'-Triazol-2'-on-5'-yl)phenyl]-3-
trifluoromethyl-5-[(3-fluoro-2'-sulfonylmethyl-[1,1']-
biphen-4-yl)aminocarbonyl]pyrazole;

5

1-[3-(2'-Amino-1',3',4'-triazol-5'-yl)phenyl]-3-
trifluoromethyl-5-[(3-fluoro-2'-sulfonylmethyl-[1,1']-
biphen-4-yl)aminocarbonyl]pyrazole;

10 1-[3-(2'-Amino-1',3',4'-triazol-5'-yl)phenyl]-3-
trifluoromethyl-5-[(3-fluoro-2'-N,N-
dimethylaminomethyl-[1,1']-biphen-4-
yl)aminocarbonyl]pyrazole;

15 1-[3-(2'-Amino-1',3',4'-triazol-5'-yl)phenyl]-3-
trifluoromethyl-5-[(3-fluoro-2'-N-pyrrolidinylmethyl-
[1,1']-biphen-4-yl)aminocarbonyl]pyrazole;

1-[3-(2'-Amino-3',4'-thiadiazol-5'-yl)phenyl]-3-
20 trifluoromethyl-5-[(3-fluoro-2'-sulfonylmethyl-[1,1']-
biphen-4-yl)aminocarbonyl]pyrazole;

1-[3-(2'-Amino-3',4'-thiadiazol-5'-yl)phenyl]-3-
trifluoromethyl-5-[(3-fluoro-2'-N,N-
25 dimethylaminomethyl-[1,1']-biphen-4-
yl)aminocarbonyl]pyrazole;

1-[3-(2'-Amino-3',4'-thiadiazol-5'-yl)phenyl]-3-
trifluoromethyl-5-[(3-fluoro-2'-N-pyrrolidinylmethyl-
30 [1,1']-biphen-4-yl)aminocarbonyl]pyrazole;

1-[3-(1',3',4'-Triazol-2'-on-5'-yl)phenyl]-3-
trifluoromethyl-5-[4-(2'-(N,N-
dimethylamino)methylimidazol-1'-yl)-2-
35 fluorophenyl)aminocarbonyl]pyrazole;

1-[3-(1',3',4'-Triazol-2'-on-5'-yl)phenyl]-3-trifluoromethyl-5-[4-(2'-methylimidazol-1'-yl)-2-fluorophenyl]aminocarbonyl]pyrazole;

5

1-[3-(Pyrid-3'-yl)phenyl]-3-trifluoromethyl-5-[(3-fluoro-2'-sulfonylmethyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole;

10 1-[3-(Pyrid-3'-yl)phenyl]-3-trifluoromethyl-5-[(3-fluoro-2'-N,N-dimethylaminomethyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole;

15 1-[3-(Pyrid-3'-yl)phenyl]-3-trifluoromethyl-5-[(3-fluoro-2'-N-pyrrolidinylmethyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole;

20 1-[3-(Pyrid-4'-yl)phenyl]-3-trifluoromethyl-5-[(3-fluoro-2'-N,N-dimethylaminomethyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole;

25 1-[3-(Pyrid-4'-yl)phenyl]-3-trifluoromethyl-5-[(3-fluoro-2'-N-pyrrolidinylmethyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole;

1-[3-(Pyrid-4'-yl)phenyl]-3-trifluoromethyl-5-[(3-fluoro-2'-sulfonylmethyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole;

30 1-[3-(5-Amino-1,3,4-oxadiazol-2-yl)phenyl]-N-{2'-[(dimethylamino)methyl]-3-fluoro-1,1'-biphenyl-4-yl}-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide;

35 1-[3-(5-Amino-1,3,4-oxadiazol-2-yl)phenyl]-N-(3-fluoro-2'-{[(3S)-3-hydroxy-1-pyrrolidinyl]methyl}-1,1'-biphenyl-

4-yl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide;
and,

1-[3-(5-Amino-1,3,4-oxadiazol-2-yl)phenyl]-N-(3-fluoro-2'-
5 {[(3S)-3-hydroxy-1-pyrrolidinyl]methyl}-1,1'-biphenyl-
4-yl)-5-(trifluoromethyl)-1H-pyrazole-3-carboxamide;

or a pharmaceutically acceptable salt thereof.

10

8. A pharmaceutical composition, comprising: a
pharmaceutically acceptable carrier and a therapeutically
effective amount of a compound of Claim 1, 2, 3, 4, 5, 6, or
7 or a pharmaceutically acceptable salt form thereof.

15

9. A method for treating or preventing a thromboembolic
disorder, comprising: administering to a patient in need
thereof a therapeutically effective amount of a compound of
20 Claim 1, 2, 3, 4, 5, 6, or 7 or a pharmaceutically
acceptable salt form thereof.

10. A compound of Claim 1, 2, 3, 4, 5, 6, or 7 for use
25 in therapy.

11. Use of a compound of Claim 1, 2, 3, 4, 5, 6, or 7
for the manufacture of a medicament for the treatment of a
30 thromboembolic disorder.

INTERNATIONAL SEARCH REPORT

In tional Application No
PCT/US 01/20112

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D403/10 C07D417/10 C07D403/14 C07D417/14 C07D401/10
C07D413/10 C07D413/14 A61K31/41 A61K31/44 A61P7/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	WO 98 28269 A (DUPONT MERCK) 2 July 1998 (1998-07-02) page 1, line 1 -page 3, line 33; claims; examples	1,8-11
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

15 November 2001

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

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PCT/US 01/20112

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
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